Progress in Neurobiology 96 (2012) 136–163

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Sex hormone activity in alcohol addiction: Integrating organizational and activational effects

Bernd Lenz [a,*], Christian P. Müller [a], Christina Stoessel [a], Wolfgang Sperling [a], Teresa Biermann [a], Thomas Hillemacher [b], Stefan Bleich [b], Johannes Kornhuber [a]

[a] Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany
[b] Center for Addiction Research (CARe), Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany

ARTICLE INFO

Article history:
Received 31 July 2011
Received in revised form 3 November 2011
Accepted 8 November 2011
Available online 18 November 2011

Keywords:
Sex hormones
Testosterone
Handedness
Lateralization
2D:4D ratio
Androgen receptor
Aromatase
Alcohol addiction
Alcohol dependence
Addiction

ABSTRACT

There are well-known sex differences in the epidemiology and etiopathology of alcohol dependence. Male gender is a crucial risk factor for the onset of alcohol addiction. A directly modifying role of testosterone in alcohol addiction-related behavior is well established.

Sex hormones exert both permanent (organizational) and transient (activational) effects on the human brain. The sensitive period for these effects lasts throughout life. In this article, we present a novel early sex hormone activity model of alcohol addiction. We propose that early exposure to sex hormones triggers structural (organizational) neuroadaptations. These neuroadaptations affect cellular and behavioral responses to adult sex hormones, sensitize the brain's reward system to the reinforcing properties of alcohol and modulate alcohol addictive behavior later in life. This review outlines clinical findings related to the early sex hormone activity model of alcohol addiction (handedness, the second-to-fourth-finger length ratio, and the androgen receptor and aromatase) and includes clinical and preclinical literature regarding the activational effects of sex hormones in alcohol drinking behavior. Furthermore, we discuss the role of the hypothalamic-pituitary-adrenal and -gonadal axes and the opioid system in mediating the relationship between sex hormone activity and alcohol dependence.

We conclude that a combination of exposure to sex hormones *in utero* and during early development contributes to the risk of alcohol addiction later in life. The early sex hormone activity model of alcohol addiction may prove to be a valuable tool in the development of preventive and therapeutic strategies.

Contents

Abbreviations: AAS, anabolic-androgenic steroids; ACTH, adrenal corticotropin hormone; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AMS, antenatal maternal stress; AR, androgen receptor; BMI, body mass index; CA1, Cornu Ammonis area 1; COMT, catechol-O-methyltransferase; CRH, corticotropin-releasing hormone; DA, dopamine; 5-DHEA, 5-dehydroepiandrosterone; DHT, dihydrotestosterone; EGCG, epigallocatechin gallate; ESR, estrogen receptor; FAS, fetal alcohol syndrome; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; NO, nitric oxide; OCDS, obsessive compulsive drinking scale; PMS, premenstrual syndrome; POMC, pro-opiomelanocortin; PR, progesterone receptor; SERM, selective estrogen receptor modulator; SHBG, sex hormone binding globulin; SN, substantia nigra; SRD5A1/2, 5-α reductase 1/2; VTA, ventral tegmental area; 2D:4D ratio, second-to-fourth-finger length ratio; 2D:4Dr-l, difference in 2D:4D ratios between the right and the left hands.

* Corresponding author at: Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Schwabachanlage 6-10, D-91054 Erlangen, Germany. Tel.: +49 913 1853 3001; fax: +49 913 1853 4105.
E-mail address: bernd.lenz@uk-erlangen.de (B. Lenz).

0301-0082
doi:10.1016/j.pneurobio.2011.11.001

1. Introduction

Alcohol addiction is characterized by a high degree of clinical heterogeneity, which is based on an even greater diversity of the involved neurocircuitries and neuronal systems. Until today, it is not possible to relate unique molecular pathomechanisms to individual patients. However, this goal remains important and carries implications for the development of a successful, individualized treatment algorithm.

The bio-psycho-social model of alcohol dependence suggests that its establishment and manifestation is controlled by a complex interaction of genetics, neurobiology, physiology, and social and environmental characteristics (e.g., chronic stress, lack of control over the putative stressors, degree of coping ability and availability of social support) (Cloninger et al., 1981; Devor and Cloninger, 1989; Knopik et al., 2004; Merikangas et al., 1998; Merikangas and Avenevoli, 2000; Witt, 2007). The subtle balance of risk and protective factors determines whether an individual develops alcohol addiction.

By the 1970s, studies had shown that the brain is a target tissue for steroidal regulation, indicating a potential role of sex hormone activity in the pathophysiology of psychiatric diseases (Stumpf and Sar, 1976). There is robust evidence for sex differences in the epidemiology, etiopathology and course of alcohol dependence. This includes the initiation and escalation of the disease, withdrawal, relapse and treatment. With the exception of testosterone, however, the role of sex hormone activity in alcohol addiction has received surprisingly little attention given the close relationship between alcohol-related behavior and the psychological traits that are controlled by sex hormones, such as impulsiveness, aggression (Archer, 1991; Eriksson et al., 2003; von der Pahlen et al., 2002), antisocial behavior/personality (Buydens-Branchey et al., 1989; Dabbs and Morris, 1990; Moeller and Dougherty, 2001), sensation seeking (Zuckermann et al., 1980), harm avoidance and depression (Berner et al., 1986). Our recent clinical association studies identified links between both alcohol dependence and addictive behaviors and traits such as handedness (Sperling et al., 2000, 2010), the second-to-fourth-finger length ratio (2D:4D ratio) (Kornhuber et al., 2011), and genetic polymorphisms of the androgen receptor (AR) (Lenz et al., 2009, 2010) and the enzyme aromatase (CYP19A1) (Lenz et al., 2011a). These characteristics are associated with both prenatal and lifetime sex hormone exposure, suggesting a common pathophysiological mechanism. Sex hormone activity strongly influences an individual's behavior and the constitution of the brain (Arnold and Breedlove, 1985; Arnold, 2009). Moreover, sex hormones play important roles in the differentiation of behavioral responses to alcohol. At present, it is not clear to what extent sex hormone-induced permanent (organizational) and transient (activational) effects, and the complex interaction of these effects, contribute to one's vulnerability to alcohol addiction.

In this article, we review the literature regarding the role of sex hormones in human alcohol dependence, including findings from animal and cell-based models. In addition, we integrate the early sex hormone activity model and introduce a novel perspective for future alcohol addiction research. We argue that the organizational effects of sex hormones sensitize the cerebral reward system to the reinforcing properties of alcohol. Because considerable pharmacological and non-pharmacological strategies already exist, this area of research has implications for the development of future preventive and therapeutic strategies.

2. Sex differences in alcohol drinking and related effects

Pathological alcohol use is a devastating public health issue. Alcohol consumption is one of the leading preventable causes of death worldwide. The recent "Global Status Report on Alcohol and Health" published by the World Health Organization (2011) states that the use of alcohol is responsible for approximately 2.5 million deaths per year. The consequences of alcohol dependence do not exclusively concern the individual, but through the high costs required to treat alcohol-induced disorders, such as

pancreatitis, liver disease and neoplasia, affect the community as well.

Research over the past 30 years has revealed distinct gender dimorphisms in alcohol addiction. These differences are related to drinking behavior, the amount of alcohol consumed, the physiological and behavioral consequences of addiction, the metabolism of alcohol, and the underlying molecular pathomechanisms.

2.1. Alcohol use and effects

Among humans, males generally drink more alcohol than females and are particularly prone to drinking in excess (Wilsnack et al., 1984). At the same time, males display less impairment of motor coordination and information processing capacity in response to alcohol (Miller et al., 2009). They are four times more likely to suffer from weekly episodes of heavy drinking, alcohol abuse, alcohol addiction and related complications than women (Ceylan-Isik et al., 2010; Greenfield and Rogers, 1999; Harford et al., 1992; WHO, 2011; Wilsnack and Wilsnack, 2002). Alcohol accounts for 6.2% of all deaths in males compared to 1.1% in females. It is the leading lethal risk factor in males between the ages of 15 and 59 years (WHO, 2011). By contrast, women are more vulnerable to the physiologically harmful effects of excessive alcohol consumption. They experience these detrimental effects more rapidly and more severely than men. As compared with men, women develop alcohol-induced cardiomyopathy, peripheral neuropathy, brain shrinkage and cognitive dysfunction after fewer years of drinking (Hommer, 2003; Prendergast, 2004). However, women show fewer and less severe withdrawal symptoms, such as tremors and anxiety (Deshmukh et al., 2003; Devaud et al., 2006).

Although preclinical and clinical findings generally agree, there are also interesting differences. Alcohol preference in free feeding male rhesus monkeys is more stable than in females (Grant and Johanson, 1988). Male rats are quicker to develop dependence and slower to recover. They suffer from more withdrawal symptoms and greater seizure susceptibility than females (Devaud and Chadda, 2001; Varlinskaya and Spear, 2004). However, female animals consume more alcohol than males (Chester et al., 2008; Juárez and Barrios de Tomasi, 1999; Lancaster and Spiegel, 1992; Lancaster et al., 1996; Sluyter et al., 2000; Strong et al., 2010; Tambour et al., 2008), an effect eliminated by gonadectomy (Almeida et al., 1998; Cailhol and Mormède, 2001). This finding is unexpected, given the previously reported opposite relationship in humans, but suggests that social factors compete with biological mechanisms. Interestingly, these sex differences are not limited to alcohol consumption but also include the initiation and escalation of the use and addiction to illicit drugs, such as cocaine. Sex differences are also found in the context of relapse following periods of abstinence (Becker and Hu, 2008). These findings indicate that sex hormone activity modulates addictive behavior in general.

2.2. Alcohol degradation

Alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) control hepatic alcohol detoxification by a two-step oxidation of ethanol to acetaldehyde and acetic acid. Acetaldehyde binds to proteins and becomes a Schiff base. Such adducts cause ethanol-linked organ damages (Nakamura et al., 2003). The rate of alcohol degradation determines the bio-availability of ethanol and acetaldehyde in the brain. Genetic variants of ADHs and ALDHs, which increase acetaldehyde either by a more rapid oxidation of ethanol or a slower oxidation of acetaldehyde, have a protective effect on the risk of alcohol dependence which is presumably due to the highly aversive effect of acetaldehyde (Edenberg, 2007; Müller et al., 2010). Thus, sexual dimorphisms in alcohol degradation are important when attempting to clarify sex differences in alcohol addiction. Dettling et al. (2007) found a higher ethanol degradation rate in healthy women than in men, though the difference disappeared after correction for liver weight. Eriksson et al. (1996) found an association between elevated acetaldehyde and higher estrogen levels in women, which was suggested to account for the sex differences in both prevalence of alcohol addiction and associated harmful effects. In line with preclinical data, these studies indicate that men and women differ in the activity of degradation-related enzymes. Female C3H/He mice show a higher rate of alcohol degradation than males. The administration of estradiol to males increases the activity of relevant enzymes, and testosterone decreases enzymatic activity in females (Kishimoto et al., 2002). The data on human sex differences in enzymatic activity of hepatic ethanol degradation is, however, inconsistent, because another study found no gender dimorphism of hepatic ADH III activity which is the main form in the liver (Chrostek et al., 2003). Altogether, most of the studies suggest that sex hormone activity influences the degradation rate of alcohol which might underlie the relationship between sex hormone activity, alcohol addiction and associated harmful effects.

2.3. Puberty and maturation: sex hormone activity and alcohol drinking gain importance

The consumption of alcohol increases substantially during late adolescence, a period of distinct sex hormone-driven neurodevelopmental changes. Adolescence is associated with a propensity towards experimentation with addictive substances and an elevated vulnerability to addictive behaviors (Chambers et al., 2003), suggesting a modifying role of sex hormones in the initiation of alcohol misuse.

As shown by epidemiological surveys in America (Schulte et al., 2009) and Europe (European School Survey Project on Alcohol and Other Drugs [ESPAD]; Hibell et al., 2009; Lavikainen et al., 2008), boys do not differ from girls in alcohol drinking patterns (e.g., lifetime alcohol use, drunkenness) during early adolescence. However, a plethora of clinical and preclinical studies point to an enhanced vulnerability to developing alcohol addiction during late adolescence (Spear, 2000). In humans, hazardous patterns of alcohol consumption, such as high-volume binge drinking, alcohol abuse and alcohol dependence, peak at the age of 18–29 in males and 16–39 in females, and decrease thereafter (Hill and Chow, 2002). Sex-specific patterns concerning alcohol dependence clearly diverge by age 18 (Knopik et al., 2004; Young et al., 2002), suggesting that the timing and progression of sexual maturation represents an important factor for the initiation of early alcohol abuse. Indeed, epidemiological approaches (Harrell et al., 1998; Lanza and Collins, 2002; Marklein et al., 2009; Tschann et al., 1994; Wilson et al., 1994) and twin studies (Dick et al., 2000) show that boys and girls who mature relatively early are more likely to drink to intoxication and to begin smoking at an earlier age than those who mature later. This result is supported by the finding that the timing of sexual maturation has predictive power for alcohol drinking in late adolescence (Bratberg et al., 2005). Furthermore, the particular vulnerability to alcohol addiction-related behavior during puberty is supported by preclinical findings in rodents showing that the acquisition of alcohol self-administration is more rapid in adolescents than in adults (Bell et al., 2006; Brunell and Spear, 2005; Doremus et al., 2005).

The link between puberty and alcohol abuse is believed to primarily be the result of social and environmental factors (Fillmore et al., 1995; King et al., 2003), such as peers, gender roles and expectations. This is a reasonable conclusion given that alcohol facilitates social interactions and sexual behavior, underscoring its utility and attractiveness for human adolescents (Beck

and Treiman, 1996; Kuntsche et al., 2005; Müller and Schumann, 2011). The number of friends smoking within the peer group is related to the individual's use of alcohol, cigarettes and marijuana (Marklein et al., 2009). Lower socioeconomic status and educational levels are associated with higher risk of alcohol-related death, disease and injury. This effect is greater for men than for women (WHO, 2011). However, these social factors may be superimposed on sex-based biology. Sex differences in alcohol preference and the drinking patterns of rats develop during the early postpubertal period (Lancaster et al., 1996), suggesting that similar biological mechanisms may underlie sex differences in adolescent alcohol consumption across species (Spear, 2000; Witt, 2007). There is a great deal of overlap between the excitatory and inhibitory neurotransmitter systems modulated by alcohol (Faingold et al., 1998; Spanagel, 2009) and the neuronal excitability induced by sex hormones (Rupprecht and Holsboer, 1999a,b). For instance, pubertal age and sex hormone activity have been demonstrated to influence the responsiveness of the NMDA receptor (Romeo et al., 2005) and the benzodiazepine/GABA receptor complex to environmental challenge in rats (Primus and Kellogg, 1991). Importantly, alcohol interacts with both receptors (Spanagel, 2009). At the level of GABAergic interneurons in the ventral tegmental area (VTA), alcohol-induced effects are followed by a disinhibition of dopaminergic neurons (Sulzer, 2011), which entails addictive pathology.

Summarizing human and animal studies, it can be concluded that not only social and psychological but also biological sex hormone-linked factors contribute to an elevated risk for the development of pathological addictive behavior during adolescence.

2.4. Alcohol-induced effects on brain reinforcement systems

Addictive drugs have the ability to produce long-lasting adaptations in neural systems. The principle underlying addiction appears to be these drugs' capacity to enhance dopamine (DA) release in the mesolimbic pathway (Di Chiara et al., 2004). This molecular mechanism is believed to play an important role in the reinforcement of drug-seeking and consumption behavior (Sulzer, 2011; Wise, 2002, 2004). The mesolimbic pathway contains dopaminergic neurons. These project from the VTA to the nucleus accumbens, which forms the dominant portion of the ventral striatum (Dalley and Everitt, 2009; Le Moal and Simon, 1991). Spiraling projections from the nucleus accumbens reach the dorsal striatum via the substantia nigra (SN) (Haber et al., 2000; Porrino et al., 2004). This pathway was shown to be important for the transition of drug-seeking from a goal-directed to a stimulus-controlled habitual behavior (Belin and Everitt, 2008; Belin et al., 2009; Everitt et al., 2001). These neuroanatomical loci have also been shown to be associated with the desire and reward mechanisms that generate psychological states such as "liking" and "wanting" (Berridge et al., 2010). Correspondingly, alcohol intake increases DA levels in the nucleus accumbens (Boileau et al., 2003; Di Chiara and Imperato, 1988a), which is known to be involved in alcohol's reinforcing effects (Diana et al., 1993).

The reinforcing properties of alcohol vary between men and women, implying that sex hormone activity affects the sensitization of brain reward circuitries to alcohol. This effect may account for the distinct gender dimorphisms in alcohol-induced effects and alcohol addiction. Males and females differ in their mesolimbic response to alcohol. PET studies show that the administration of 1 ml/kg alcohol to healthy humans promotes cerebral DA release with a preferential effect in the ventral striatum (Boileau et al., 2003). This effect is twice as strong in men as in women. Furthermore, only in males is the striatal DA release correlated with the measures of subjective alcohol-induced activation (Urban et al., 2010). Moreover, alcohol-induced changes in nucleus accumbens DA levels are negatively associated with later alcohol intake in male but not female rats (Blanchard et al., 1993; Blanchard and Glick, 1995).

Several direct and indirect mechanisms have been suggested for the alcohol-dependent DA release in the VTA, such as indirect activation of VTA neurons via nicotinic acetylcholine receptors (Ericson et al., 2003) and an increase of VTA glutamate release (Xiao et al., 2009). In addition, alcohol modulates GABAergic feedback in the VTA, thereby disinhibiting mesolimbic dopaminergic neurons (McBride et al., 1999; Spanagel, 2009; Sulzer, 2011). Interestingly, the activation of μ-opioid receptors on GABAergic VTA projection neurons is capable of modulating the alcohol-induced DA response. This activation was suggested to be an important mechanism underlying alcohol addiction (Xiao and Ye, 2008). Appropriately, the μ-opioid receptor is primarily responsible for the reinforcing properties of drugs (Contarino et al., 2002; Di Chiara and Imperato, 1988b).

There is direct evidence from preclinical studies that both androgens (Alderson and Baum, 1981; de Souza Silva et al., 2009; Hernandez et al., 1994) and estrogens (Di Paolo et al., 1985; Lammers et al., 1999; Landry et al., 2002; McEwen, 2002) are able to trigger a DA response in the mesolimbic pathway, in particular in the nucleus accumbens. This action explains the addictive potential of anabolic-androgenic steroids (AAS). Estradiol increases the mesolimbic DA reuptake site density (Morissette et al., 1990; Morissette and Di Paolo, 1993a,b) and the number of D1 and D2 receptors (Lévesque and Di Paolo, 1991). Accordingly, ovariectomized rats show altered D2 receptor expression in the striatum (Gordon and Fields, 1989). These findings are relevant to addiction given that D2 receptor expression is linked to drug-seeking behavior (De Vries et al., 2002). In essence, sex hormones and alcohol converge in their effect of increasing mesolimbic DA release. Potential mechanisms include the hypothalamic-pituitary-adrenal (HPA) and -gonadal (HPG) axes as well as interactions with the endogenous opioid system.

The HPA axis modulates the reinforcing effects of alcohol. The major function of the HPA axis is mediating the organism's physiological reaction to stress. The 21-carbon corticosteroid corticosterone is produced in the cortex of the adrenal gland upon HPA axis activation. In rats, the intravenous self-administration of this hormone has reinforcing properties (Piazza et al., 1993). The levels of corticosterone associate positively with the amount of alcohol consumed by male rats (Fahlke et al., 1994a, 1995). Female rats develop higher blood levels of corticosterone than males following alcohol intake (Silveri and Spear, 2004). This may account for the observation that men require more alcohol than women to achieve a rewarding effect of alcohol (Witt, 2007).

Furthermore, there is evidence that the opioid system modulates the relationship between sex hormone activity and the reinforcing effects of alcohol. Endogenous opioids and their related receptors are found ubiquitously in the mesolimbic system. The opioid system mediates reward by influencing dopaminergic activity (Trigo et al., 2010). There is a bidirectional interrelation between sex hormones and the opioid system in that opioids actively affect sex hormone levels and in turn endogenous opioids are passively affected by sex hormones (Section 5.5.2). This is illustrated indirectly by human gender differences with respect to pain and the antinociceptive effects of opioid receptor modulators (Gear et al., 1996a,b, 2003; Manson, 2010; Sarton et al., 2000; Zacny, 2001). Direct prove is provided by opioid-induced changes of cellular steroid synthesis, gonadal function as well as brain and peripheral sex hormone levels (Amini and Ahmadiani, 2005; Ceccarelli et al., 2006; Jenab and Morris, 2000; Katz and Mazer, 2009; Pirnik et al., 2001) and by sex hormone-induced modulation of endogenous opioids and related receptors in preclinical studies

(Hammer and Bridges, 1987; Hammer et al., 1993; Pluchino et al., 2009b; Zhou and Hammer, 1995).

In summary, the reinforcing properties of alcohol are sex specific. Sex hormone activity causes neuroadaptive changes, sensitizing the brain's reward circuitries to the reinforcing properties of alcohol. Pathways mediating these effects include the HPA and HPG axes as well as the opioid system.

3. The addictive potential of sex hormones: the role of anabolic-androgenic steroids

AAS, such as testosterone and nandrolone, provide direct proof of the addictive potential of male sex hormones. Testosterone and its synthetic derivatives are used by athletes in order to enhance their performance and appearance (Dyment, 1987; Müller and Schumann, 2011). Several studies report that approximately a third of all AAS users meet the DSM (-III or -IV) criteria for substance dependence (Kanayama et al., 2010), supporting the idea that male sex hormones are potentially addictive (Brower et al., 1991; Kanayama et al., 2009). AAS exert psychoactive effects, including reward, euphoria (Kashkin and Kleber, 1989) and aggressive behavior (Kouri et al., 1995; Pope et al., 2000). Hence, the high comorbidity of AAS use with other addictive disorders (DuRant et al., 1993), such as alcohol or opioid dependence, is not surprising. AAS users are at particular risk for having an inebriation-oriented lifestyle (Mattila et al., 2010) and for suffering from opioid abuse (Arvary and Pope, 2000; Wines et al., 1999). AAS withdrawal symptoms are similar to those of opioid withdrawal (Kashkin and Kleber, 1989) and may be provoked by opioid antagonists (Tennant et al., 1988). Moreover, simultaneous AAS use reduces the threshold for heroin overdose (Thiblin et al., 2000).

In animal models, repeated infusions of testosterone induce physical and behavioral tolerance, which is one of the major criteria for dependence according to the DSM-IV and ICD-10. Hamsters self-administer testosterone, occasionally even in lethal doses (Wood, 2006). In male rats, the administration of the AAS nandrolone decanoate effects similar modulation on brain opioid peptides and addictive behavior. It increases β-endorphin levels in the VTA and reduces dynorphin B levels in the nucleus accumbens which hypothetically promotes the rewarding effects of ethanol. And indeed, rats treated with nandrolone decanoate show enhanced voluntary alcohol intake and aggressive behavior (Johansson et al., 1997, 2000). The administration of the opioid antagonist naltrexone prevents the reinforcing effects of testosterone in a self-administration paradigm (Peters and Wood, 2005). AAS intoxication in hamsters resembles opiate intoxication, including central nervous system (CNS) depression and reductions in locomotion, respiration and body temperature. These effects can be abolished by naltrexone (Peters and Wood, 2005). Altogether, several lines of evidence suggest that male sex hormones cause addictive behavior by a mechanism involving the opioid system.

4. The sex hormone axis: from the hypothalamus to cellular effects

4.1. The hypothalamic-pituitary-gonadal axis

In general, the term "sex hormone" is used as a synonym for "sex steroid", "gonadal steroid" and "gonadal hormone". Gonadal sex hormones are androgens, estrogens and progestagens. However, they are not only produced in the gonads but also in the cortex of the suprarenal gland and in placental tissue. Their secretion is regulated by a hierarchy of hypothalamic and pituitary hormones (Fig. 1). Gonadotropin-releasing hormone (GnRH) is synthesized and released from neurons within the hypothalamus.

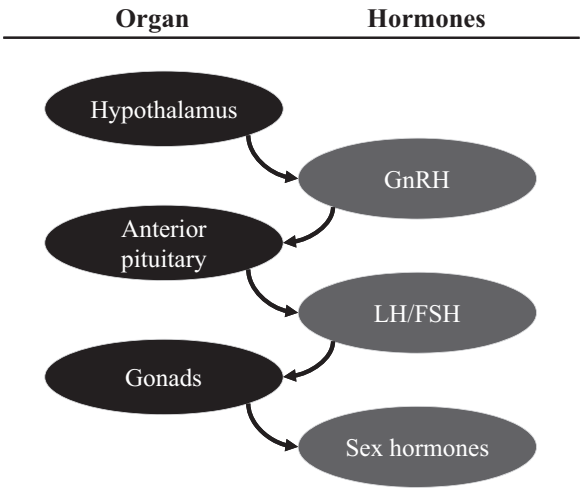

Fig. 1. The hypothalamic-pituitary-gonadal axis. GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

It induces the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. These two hormones regulate the levels of sex hormones which are derived from cholesterol in the male testes, the female ovaries and in small amounts in the adrenal glands (Fig. 2). Testosterone is the male sex hormone and has anabolic properties, such as the growth of muscle, bone and body hair. It is reduced into dihydrotestosterone (DHT) (Bruchovsky and Wilson, 1968), which increases its affinity to the AR. Estrone and estradiol influence reproductive and sexual functioning in men and women and affect other organs, such as the bones. Progesterone regulates the female menstrual cycle and pregnancy.

Alcohol interferes with sex hormone activity by promoting the aromatization of androgens during estrogen biosynthesis (Purohit, 2000). It therefore influences the androgen/estrogen ratio. However, there are several other mechanisms that mediate the relationship between alcohol intake and sex hormones. These are described below in further detail (Section 5.3).

4.2. Cellular signaling of sex hormones

The term "sex hormone axis" as used here includes the HPG axis and the units necessary for the cellular down-stream signaling of sex hormones, such as sex hormone receptors, biosynthesis and degradation. To fully appreciate neuronal responses to sex hormones, we need to understand the intricate regulation of the enzymes that catalyze their metabolism and the complex modulation of their receptors. As such, sex hormone signaling may be impaired at a minimum of six different levels: biosynthesis, receptor binding, tissue responsiveness, receptor activity, transcription and translation (Carruthers, 2008).

Two different mechanisms of cellular sex hormone activity are known. The classical "genomic" mechanism is the entry of sex hormones into cells by passive diffusion, where they allosterically activate their specific nuclear receptor(s). Testosterone binds to the AR, estrogen binds to either nuclear estrogen receptor 1 (ESR1) or 2 (ESR2) (Mosselman et al., 1996; Walter et al., 1985), and progesterone binds to the progesterone receptor (PR) (Mani, 2006). Each sex hormone receptor shows a specific expression pattern in different brain tissues. For instance, ARs were found in the human and rat hippocampus (Beyenburg et al., 2000; Kerr et al., 1995), and in the VTA, the SN and other midbrain neurons projecting to the nucleus accumbens in rats (Creutz and Kritzer, 2004; Kritzer, 1997). ESRs are widely distributed in dopaminergic midbrain neurons (Creutz and Kritzer, 2002), in limbic structures and in

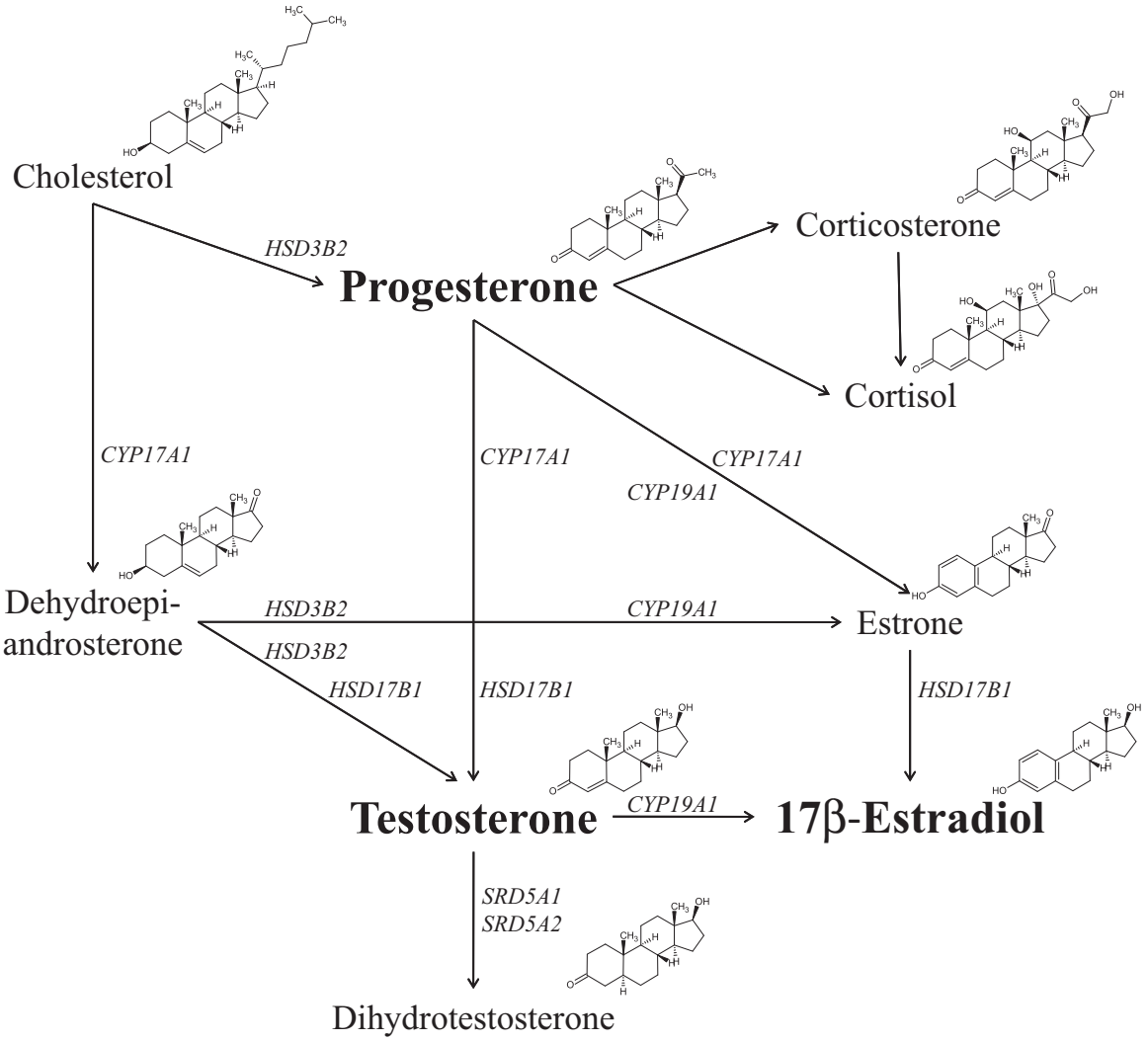

Fig. 2. Sex hormone biosynthesis. Conversions are depicted by arrows. The selected subset of implicated enzymes is italicized (Table 1).

areas associated with learning and memory (Shughrue et al., 1997). Following conformational changes, the sex hormone-receptor complex is translocated into the cell nucleus where it binds to appropriate hormone response elements on the DNA. This complex subsequently affects the transcription of specific genes (O'Malley and Tsai, 1992). The transcriptional activity of sex hormone-receptor complexes is influenced by their functional and structural interaction with a multitude of different co-activators, indicating that a wide range of cellular functions and signals converge on the sex hormone axis (Heemers and Tindall, 2007). For instance, DA signaling was reported to converge with sex hormone-initiated pathways (Mani, 2006). Intriguingly, these co-factors are capable of regulating transcription via binding to specific DNA sequences. In this way, they enable the sex hormone-receptor complexes to induce gene expression independently of their specific genomic hormone-response elements (Uht et al., 1997). A further level of complexity is the direct interaction between androgen and estrogen signaling during the early postnatal period. Estradiol regulates the expression of the AR in the developing forebrain of male rats (McAbee and Doncarlos, 1999).

In addition to the genomic mechanism of sex hormone signaling, recent studies have demonstrated a "non-genomic" mode at the membrane surface. Sex hormone activity influences the responsiveness of the benzodiazepine/GABA receptor complex to environmental challenge in rats (Primus and Kellogg, 1991). In addition, ESRs interact with metabotropic membrane-localized receptors (Boulware and Mermelstein, 2009; Kelly et al., 2003; Mermelstein and Micevych, 2008; Mermelstein, 2009). ARs regulate the activity of different kinases and control the phosphorylation of intracellular proteins, influencing their molecular activity (Bennett et al., 2010). 17β-Estradiol stimulates the membrane estrogen receptor (Gq-mER), thereby activating phospholipase C. This subsequently results in the up-regulation of protein kinase A and C (Roepke et al., 2009). These non-genomic and more rapid mechanisms may explain why some sex hormone-induced effects are incompatible with the slower time course of genome-initiated events (Foradori et al., 2008; Papadopoulou et al., 2009).

Sex hormones have been shown to potently modulate the neurotransmitter systems that are associated with the brain's reward circuitry via intracellular (genomic) and membrane-bound (non-genomic) receptor-mediated mechanisms (Zheng, 2009). These effects may contribute to the neuronal mechanisms by which sex hormone activity regulates addiction-related behaviors.

4.3. The activational and organizational effects of sex hormones

Sex hormones exert both permanent and transient effects throughout life. In 1959, Phoenix et al. showed for the first time that "organizational" effects of sex hormones lead to irreversible

structural and functional changes of the body and brain, with subsequent long-term behavioral effects. For example, girls and boys differ in the rate at which gray and white brain matter grow during puberty (De Bellis et al., 2001; Giedd et al., 1999, 2006, 2009; Lenroot and Giedd, 2006; Lenroot et al., 2007), a fact that might be explained by the neurotrophic roles of androgens in promoting fiber outgrowth and sprouting (Morse et al., 1992). Organizational effects are not only caused by testosterone but also by estradiol, which is formed from the aromatization of androgens (de Jonge et al., 1988; Schulz et al., 2009a). Research in the 1970s demonstrated a maximally sensitive period for organizational effects of sex hormones during late prenatal and early neonatal development (Baum, 1979; Schulz et al., 2009a). New clinical and preclinical studies indicate that the period of sex hormone-dependent organization does not end until adulthood. In addition to the pre- and perinatal periods, adolescence, during which children become adults at intellectual, physical, hormonal, and social levels, is a period of elevated vulnerability. An investigation using a test of spatial cognition in which men normally perform better than women reported that males who were exposed to low levels of sex hormones before puberty performed worse when compared to those with normal pubertal exposure. Similarly, males with low prepubertal sex hormone levels performed worse than those who developed hypogonadotropic hypogonadism during adulthood (Hier and Crowley, 1982). These findings underscore that puberty represents a period of sensitivity to the organizational effects of sex hormones. This association was further confirmed by results from the Syrian hamster model that suggested a causal relationship; castration prior to puberty causes a reduction in aggressive behavior that cannot be restored even by prolonged testosterone replacement in adulthood (Schulz et al., 2004). In addition, there are several rodent studies that provide evidence for the organizational effects of sex hormones during puberty (Eichmann and Holst, 1999; Pellis, 2002; Shrenker et al., 1985). Because early exposure has a greater impact on behavior than later exposure, it appears that organizational mechanisms are relevant from early gestation until adulthood, with steadily decreasing sensitivity (Schulz et al., 2009a,b) (Fig. 3). In summary, the organizational effects of sex hormones may both potentiate and limit human behavioral and cellular responses to adult sex hormone exposure (Lenz and McCarthy, 2011), thereby setting the parameters within which postpubertal sex hormones operate.

Effects that are reversible and directly mediated by sex hormones are termed "activational". For example, androgens prevent heat-shock-induced hyperphosphorylation of the tau protein (Papasozomenos, 1997). However, the distinction between the activational and organizational effects of sex hormones is not absolute (Arnold and Breedlove, 1985). For instance, androgens have been reported to protect against oxidative stress (Ahlbom et al., 2001) and apoptosis (Hammond et al., 2001). It is not possible to determine whether these effects are due to the activational or organizational effects of sex hormones.

In summary, sex differences reflect the complex interaction between the permanent organizational and transient activational effects of sex hormones (Arnold, 2009; Sisk and Zehr, 2005; Weinberg et al., 2008). The available evidence suggests that the organizational effects of sex hormones contribute to the development of alcohol addiction via the sensitization of brain reward circuits to alcohol-induced reinforcement.

5. The hypothalamic-pituitary-gonadal axis and alcohol addiction

Sex hormone levels affect voluntary alcohol intake. In turn, alcohol consumption alters sex hormone levels. Hence, the relationship between sex hormones and alcohol consumption is bidirectional. This implies that the impact of one factor on the other may shift during the course of alcohol addiction (Fig. 4a and b).

5.1. Human studies

In healthy male college students, higher testosterone levels are associated with increased alcohol consumption (La Grange et al., 1995). Males with high testosterone levels are more frequently intoxicated, more likely to binge drink and more frequently diagnosed with alcohol dependence than males with low testosterone levels (Eriksson et al., 2005; Suzuki et al., 2009). Accordingly, in dependent populations, alcohol abstinence co-occurs with elevated testosterone, estradiol and LH concentrations (Hasselblatt et al., 2003; King et al., 1995). Interestingly, the effects of alcohol withdrawal and tobacco on testosterone levels are cumulative. Extensive smoking of alcohol-dependent patients leads to an additional increase in testosterone levels during withdrawal (Walter et al., 2007), indicating a common pathophysiological mechanism. However, the majority of human addiction studies have primarily focused on male patients. There are few clinical trials that have attempted to illuminate the sex hormone/alcohol dependence relationship in women. Both higher testosterone and estradiol levels are associated with a greater likelihood of current alcohol use in adolescent, pre- and postmenopausal women (Martin et al., 1999; Muti et al., 1998; Purohit, 1998). Similarly, long-term use of oral contraceptives ($\geq$5 years) is linked to increased alcohol consumption (Lund and Jacobsen, 1990). Women with unaltered menstrual cycles who are social drinkers report more frequent solitary drinking at menstruation, a relationship not present in women taking oral contraceptives (Sutker et al., 1983). Two studies showed higher alcohol consumption in the post- and intermenstrual phases (days 7–21) (Harvey and Beckman, 1985; Lindman et al., 1999), although another study failed to reproduce this finding (Holdstock and de

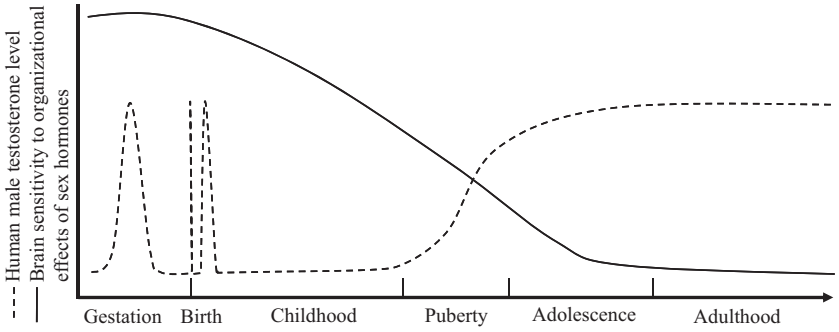

Fig. 3. Brain sensitivity to organizational effects of sex hormones throughout life. The dashed line illustrates human male testosterone levels with three distinct perinatal peaks, a mid-gestational peak and two postnatal peaks, as well as a final persistent increase during puberty (McIntyre, 2006); the solid line indicates the degree of brain sensitivity to the organizational effects of sex hormones (modified to Schulz et al., 2009a).

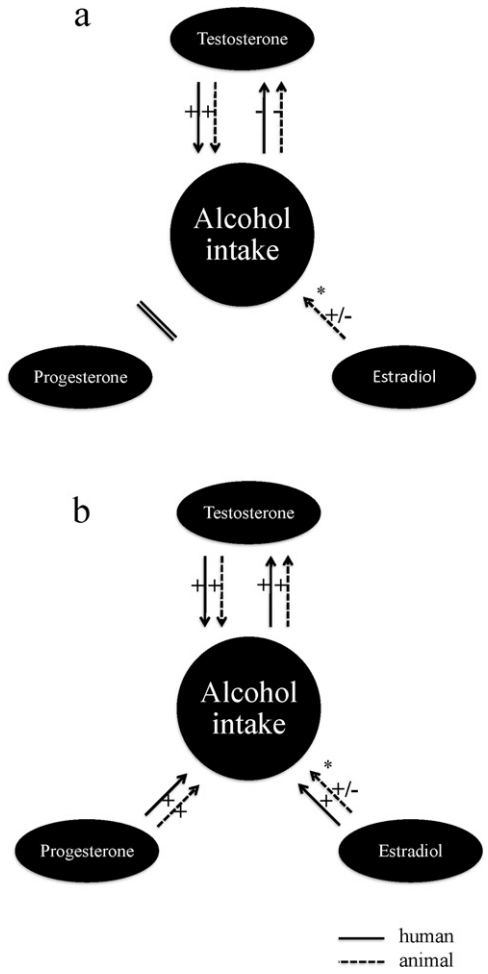

Fig. 4. The bidirectional relationship between peripheral sex hormones and alcohol intake in males (a) and females (b). Solid arrows identify human relations and dashed arrows indicate data derived from animal models. + indicates an inductive link, – an inhibitional link and || no link. * In rodents, estradiol causes an initial aversion followed by a gradually developing preference for alcohol.

Wit, 2000). In addition, premenstrual syndrome (PMS), which commonly occurs during the luteal phase, is similarly related to increased alcohol use (Mello et al., 1990). The luteal phase (days 15–28) is characterized by a reduced ability of rewarding conditions to activate the midbrain and the left fronto-polar cortex (Dreher et al., 2007), factors that may account for the increase in alcohol intake during this period. PMS is suggested to be provoked by a decline of β-endorphin (Giannini et al., 1990), suggesting a further link between elevated alcohol intake and the human opioid system. The luteal phase is associated with elevated progesterone levels. Given that females with high estradiol levels are more likely to drink alcohol (Martin et al., 1999; Muti et al., 1998), this is incompatible with the idea that estradiol and progesterone exert opposing behavioral effects. However, there is evidence that the effects of progesterone, which modulates addictive behaviors, depend on the administered dose and the length of treatment (Quinones-Jenab and Jenab, 2010).

Acute and chronic alcohol consumption induces alterations of peripheral sex hormone levels in humans. The effects are dose-dependent. Healthy males show increased peripheral testosterone levels following intake of a low dose of alcohol (Sarkola and Eriksson, 2003). By contrast, acute alcohol intoxication decreases peripheral testosterone levels (Frias et al., 2000, 2002; Mendelson et al., 1977). Similarly, many studies have consistently demonstrated an association between chronic alcohol abuse and reduced peripheral testosterone levels in males (Maneesh et al., 2006; Muthusami and Chinnaswamy, 2005). This effect can reverse during and following withdrawal (Castilla-García et al., 1987; Heinz et al., 1995; Välimäki et al., 1984). However, Walter et al. (2007) found no significant differences between alcohol-dependent patients and healthy controls in free testosterone levels at the onset of withdrawal. With respect to alcohol-induced changes of LH and FSH, clinical studies report findings which differ between acute and chronic alcohol intake. Some have reported levels of these hormones to be decreased in acute alcohol intoxicated males (Frias et al., 2002), an effect that was explained by the inhibition of the secretion of the hypothalamic GnRH and/or pituitary LH (Hiney and Dees, 1991). Alternatively, several authors have found increased LH and FSH levels in alcohol-dependent patients and interpret their finding as a negative feedback mechanism that follows alcohol-induced damage of the Leydig and Sertoli cells (Heinz et al., 1995; Lindholm et al., 1978; Muthusami and Chinnaswamy, 2005; Orpana et al., 1990; Van Thiel et al., 1983, 1987). In contrast to the alcohol-induced effects on sex hormones in males, low-dose alcohol intake (Eriksson et al., 1994) as well as acute alcohol intoxication in women is related to increased plasma testosterone levels (Frias et al., 2000, 2002; Sarkola et al., 2000).

Altogether, the relationships between human alcohol consumption, drinking cessation, testosterone, estradiol and progesterone are complex.

5.2. Limitations of human association studies

Clinical association trials examining the relationship between sex hormones and alcohol drinking should be interpreted carefully. The following points should be considered: gender and the degree of sexual maturation of the research participants; the circadian and seasonal rhythms of sex hormone secretion; the variance in the acute and chronic effects of alcohol consumption; the phenomenological heterogeneity of alcohol addiction; and the potential for bidirectionality in associational study designs.

The effects of alcohol on the HPG axis have to be considered relative to the gender investigated. Human and animal studies show that alcohol intoxication increases testosterone levels in females, whereas it induces a decrease in males (Forquer et al., 2011; Frias et al., 2002). In addition, the degree of sexual maturation impacts alcohol-induced alterations of sex hormones. Alcohol administration reduces testosterone levels in sexually mature male rats and increases them in sexually immature rats (Little et al., 1992). Sex hormone levels depend on circadian and seasonal rhythms. For instance, there is an increase in human male testosterone, LH and FSH during the summer (Dabbs, 1990a,b; de la Torre et al., 1981; Maes et al., 1997; Meriggiola et al., 1996). Moreover, studies vary in whether they measure free or total testosterone or the sex hormone binding globulin (SHBG). However, free testosterone is the biologically active fraction and closely reflects clinical situations (Vermeulen et al., 1999). It should also be considered that the effects of alcohol vary depending on whether an individual abuses alcohol acutely or chronically. However, the majority of controversial results in alcohol addiction research are most likely due to the high degree of the phenomenological and etiopathological heterogeneity of the clinical diagnosis, "alcohol dependence" according to DSM-IV or ICD-10 (cf., different typologies, e.g., Babor et al., 1992; Cloninger et al., 1981; Cloninger, 1987; Jellinek, 1960; Lesch et al., 1988; Schuckit and Irwin, 1989). Therefore, individuals with the "same" alcohol dependence may suffer from different pathologies. Studies should include large sample sizes to investigate heterogeneous groups of patients and to sufficiently consider the subtypes of alcohol addiction. Finally, determining causal relationships or even assigning the direction of an association from correlational clinical studies is challenging. This is particularly relevant when

speculating on the direction of the link between sex hormones and addiction-linked behavior. Although sex hormones modulate behavior in social interactions, aggressive actions were shown to affect androgen levels vice versa (Zitzmann and Nieschlag, 2001).

5.3. Animal studies

One advantage of animal studies is that they allow the clarification of whether associations derived from human trials reflect causal relationships. As described in the following section, most of the relationships that have been demonstrated in humans are supported by investigations in primates and rodents. Hence, the relationship between sex hormones and alcohol intake varies both according to the gender and to the direction studied (sex hormones→alcohol or alcohol→sex hormones).

Males from alcohol-preferring rat lines have higher serum testosterone levels than non-preferring lines (Apter and Eriksson, 2003). The administration of testosterone to castrated male rats increases the degree of alcohol preference. In comparison with controls, progesterone does not impact alcohol preference in castrated male rats (Lakoza and Barkov, 1980). The effects of estradiol on alcohol intake in male rodents depend on the duration of administration. Acute estradiol benzoate treatment reduces voluntary alcohol consumption in rats (Juárez et al., 2002). Administration of estradiol benzoate over 49 days has no effect (Lakoza and Barkov, 1980), whereas administration of 17β-estradiol over 60 days elevates voluntary alcohol consumption in mice (Hilakivi-Clarke, 1996). It is therefore suggested that estradiol initially produces an aversion followed by a gradually developing preference for alcohol (Marinelli et al., 2003). In most cases, behavioral experiments do not include female animals because the cyclic fluctuations of sex hormones cause "noise" in the data. This is due to variability associated with estrus, which requires great effort to be managed from an experimental standpoint. Nevertheless, the parallel investigation of both genders is indispensable, particularly because of certain sex differences in behavioral tests (Johnston and File, 1991). Female mice that are seizure-resistant during alcohol withdrawal show increased testosterone levels during periods of abstinence, an effect that is not observed in mice that are seizure-prone during withdrawal (Forquer et al., 2011). Therefore, the individual's genotype is an important determinant of sex hormone responses during abstinence. The effects of estradiol in females are similar to those of males. The acute injection of estradiol causes a cessation of alcohol intake in female rats. Consumption returns to baseline during continued daily administration over 14 days (Sandberg and Stewart, 1982; Sandberg et al., 1982). However, the effects of a continuous exposure to estradiol are equivocal. Whereas one study reported a decrease in voluntary alcohol intake following 60 days of 17β-estradiol administration in female mice (Hilakivi-Clarke, 1996), another showed that the injection of estradiol valerate, a long-acting estrogen, increases alcohol preference of female rats (Marinelli et al., 2003). Alcohol intake reaches its minimum on the days of proestrus and estrus (Forger and Morin, 1982; Roberts et al., 1998), corresponding to the acute effects of estradiol. Female macaque monkeys self-administer lower levels of alcohol at menstruation when compared to the mid-cycle or luteal phases, both periods of elevated estradiol and progesterone levels (Mello et al., 1986). These data suggest that the individual's sex hormone pattern has predictive value for alcohol intake and presumably for the development of alcohol addiction.

While sex hormones can determine alcohol preference and consumption, alcohol feeds back on the sex hormone axis once it is consumed. This effect was measured in animals following alcohol administration. The administration of alcohol to animals causes gender-, dose- and tissue-specific alterations in testosterone levels. Acute alcohol intake results in a dose-related decrease of plasma testosterone concentrations during the mating season in dominant male monkeys (Winslow and Miczek, 1988). Furthermore, a high dose of alcohol (1.5 g/kg) decreases peripheral testosterone levels in male rats (Cicero and Badger, 1977; Eriksson et al., 1983). Interestingly, this effect is more pronounced in alcohol non-preferring than in alcohol-preferring animals (Apter and Eriksson, 2003). Similarly, continuous daily administration of 3.75 g/kg of alcohol over 5 days decreases serum testosterone levels in mature male rats (Babichev et al., 1989). Alcohol inhibits the production of testicular testosterone through independent mechanisms in diverse pathways, such as nitric oxide (NO) synthesis (Adams et al., 1993), the opioid system (Apter and Eriksson, 2003, 2006; Cicero et al., 1989; Emanuele et al., 1998) and adrenergic-dependent signaling (Rivier, 1999). However, there is evidence that alcohol-induced effects on testosterone levels depend on the applied alcohol dose, the tissue and the sex investigated. The low-dose effect of alcohol is ambiguous, as studies have reported increased (Cicero and Badger, 1977) and reduced (Apter and Eriksson, 2003) testosterone levels. Contrary to the findings regarding peripheral sex hormones, Alomary et al. (2003) reported a 4-fold elevation of testosterone in the frontal cortex of male rats following a high dose of alcohol (2.0 g/kg). With respect to females, acute alcohol-intoxicated mice that are prone to seizures during withdrawal exhibit increased testosterone levels, whereas mice that are seizure-resistant during withdrawal do not (Forquer et al., 2011).

5.4. The relationship between the hypothalamic-pituitary-gonadal axis and alcohol addiction

Taken together, animal studies support and extend the reported relationships between the HPG axis and alcohol addiction observed in humans. These studies show that sex hormones influence alcohol-related behavior in different ways. Androgens and estrogens determine alcohol preference and drinking. These hormones may also induce tolerance and sensitization. Once alcohol is consumed, however, it feeds back on sex hormone activity and may subsequently affect the future influence sex hormones have on drinking behavior. The bidirectional relationship between sex hormones and alcohol dependence indicates that the role of sex hormones may change during the course of alcohol dependence. Fig. 4a and b summarizes the current knowledge of the relationship between alcohol and sex hormones in females and males. The intricate interaction of testosterone, estradiol and progesterone further complicates the prediction of how endocrinological profiles affect addictive behaviors. A knowledge of this process will require further studies on the role of sex hormone activity during the different stages of alcohol dependence, such as initiation, maintenance, withdrawal, treatment outcome and relapse.

5.5. The modulating functions of the hypothalamic-pituitary-adrenal axis and the opioid system

The bidirectional relationship between alcohol dependence and the HPG axis is modulated by other mechanisms, such as the opioid system (Apter and Eriksson, 2003, 2006; Cicero et al., 1989; Emanuele et al., 1998) and the HPA axis (Apter and Eriksson, 2003, 2006; Rivier, 1999). Both systems are implicated in the reinforcing properties of alcohol and their modifying effects on alcohol consumption are beyond doubt (Fahlke et al., 1994a,b, 1995; Gianoulakis, 2001; Heilig and Koob, 2007; Koob et al., 1998; Lamblin and De Witte, 1996; Piazza et al., 1993; Trigo et al., 2010). β-Endorphin and the adrenal corticotropin hormone (ACTH) share

the same precursor protein with pro-opiomelanocortin (POMC). Both β-endorphin and ACTH are co-stored in cells of the anterior pituitary gland and are co-released in response to various stimuli (Guillemin et al., 1977; Weber et al., 1979). The two following sections briefly outline the simultaneous impact of the HPA axis and the opioid system on the relationship between sex hormone activity and alcohol intake.

5.5.1. The hypothalamic-pituitary-adrenal axis

The human HPA axis represents a complex interaction between the brain, the anterior pituitary gland and the adrenal cortex. This axis includes corticotropin-releasing hormone (CRH), POMC, ACTH and glucocorticoids, such as cortisol (in humans) and corticosterone (in rats) (Goeders, 2002). CRH is synthesized and released from neurons of the hypothalamic paraventricular nucleus. It stimulates the anterior pituitary to secrete ACTH, which in turn enhances the release of cortisol and corticosterone from the adrenal cortex (Guillemin et al., 1977; Weber et al., 1979). The interaction between the HPG and HPA axes is bidirectional and occurs at several levels (Patchev et al., 1995; Rivier and Rivest, 1991; Viau, 2002). This is illustrated indirectly by sexual dimorphisms of HPA responsivity and directly by sex hormone-induced modulation of the HPA axis. The increase of ACTH following the administration of CRH is greater in women than in men (Gallucci et al., 1993; Heuser et al., 1994). In contrast, psychological stress induces greater HPA axis responses (ACTH and cortisol) in adult men than in women (Kirschbaum et al., 1995a, 1999; Uhart et al., 2006). This sexual dimorphism was also shown in the elderly (Kudielka et al., 1998) and acutely depressed psychiatric in-patients (Künzel et al., 2003). Women treated with 5-dehydroepiandrosterone (5-DHEA) show ACTH responsivity similar to men (Kudielka et al., 1998). The use of oral contraceptives (monophasic formulas of ethinylestradiol, <50 μg) attenuates the cortisol response (Kirschbaum et al., 1995b, 1999). Moreover, these effects differ depending on the stage of the menstrual cycle, with a peak observed during the luteal phase (Kirschbaum et al., 1999).

It is well established that the HPA axis plays a role in the onset and time course of alcohol dependence. Alcohol addicts exhibit lower ACTH and cortisol levels and blunted pituitary ACTH and cortisol responses to exogenous CRH administration. This impairment may account for the reduced response to non-alcohol-induced stress in alcohol-dependent patients (Gianoulakis et al., 2003; Wand and Dobs, 1991). The pathological HPA axis response is not limited to actively drinking individuals, but persists into periods of abstinence (Lovallo et al., 2000; Vescovi et al., 1997). Moreover, recent studies report that childhood trauma, neglect and poor parent–child attachment influence alcohol, cocaine and heroine dependence by modulating adult ACTH and cortisol levels (Gerra et al., 2008; Schäfer et al., 2010). This indicates that early "hits" cause silent alterations of the HPA axis, which become relevant for addictive behavior during adulthood. In rats, maternal behavior controls the offspring's epigenetic programming of the glucocorticoid receptor (Weaver et al., 2004). Thus, we suggest that sex hormones trigger epigenetic alterations early in life (Kumar and Thakur, 2004; Singh and Prasad, 2008) which may account for an individual's predisposition to addictive behavior in later life. Additionally, preclinical findings underscore the role of the HPA axis in alcohol dependence. In rats, the level of corticosterone, a 21-carbon corticosteroid produced in the cortex of the adrenal gland, is positively associated with the amount of alcohol consumed (Prasad and Prasad, 1995). Adrenalectomy protects against the development of alcohol preference and decreases alcohol consumption (Lamblin and De Witte, 1996). Moreover, the administration of corticosterone restores the intake of alcohol to the preoperative level (Fahlke et al., 1994a). Conversely, the application of metapyrone, which suppresses corticosterone synthesis, reduces alcohol consumption in high-preferring rats (Fahlke et al., 1994b).

Alcohol consumption in turn modulates the HPA axis. In humans, acute alcohol intoxication produces an increase in ACTH and cortisol levels, with females demonstrating a higher responsivity than males (Frias et al., 2002). This sexual dimorphism corresponds to findings from rodents where the HPA response to alcohol depends on estrogens rather than androgens (Ogilvie and Rivier, 1997).

Furthermore, the HPA axis is linked to the opioid system; there is a positive dose–response relationship between naloxone antagonism of the opioid receptor and peripheral ACTH levels (Mangold et al., 2000). This mechanism underlies a gender dimorphism, namely that females show greater hormonal reactivity than males following administration of naloxone and naltrexone (Roche et al., 2010; Uhart et al., 2006).

5.5.2. The opioid system

Opioids are the most effective and widely used drugs for the treatment of severe pain. Both the intended and the undesirable side effects are gender-dependent. Clinicians fear their addictive potential and the rapid development of tolerance. The relationship between the opioid system and the HPG axis is bidirectional and plays an important role in the modulation of addictive behavior and the pathology of alcohol dependence.

Endogenous opioids are grouped into three major classes: endorphins, enkephalins and dynorphins. These bind to their membrane-bound, cognate G protein-coupled receptors (δ, κ, μ, nociceptin). A strong interaction between the sex hormone axis and the opioid system is beyond doubt. This connection is illustrated indirectly by sex differences in the prevalence, perception and treatment outcome of human pain. Direct evidence for the connection between sex hormones and the opioid system is shown by sex hormone-dependent results following experimental modulation of endogenous opioids in rodents. Compared to men, women have a higher prevalence of severe pain conditions (Manson, 2010). Females report a greater antinociceptive benefit from lower doses of μ- and κ-opioid receptor modulators. This effect occurs with a slower speed of onset and offset in women (Gear et al., 1996a,b, 2003; Sarton et al., 2000). Following intravenous application of morphine, women score higher than men on scales measuring sensations such as "coasting (spaced out)", a "heavy or sluggish feeling" and "dry mouth" (Zacny, 2001). During the first postoperative days, males require higher doses of opioids (Chia et al., 2002). Interestingly, opioids may act as full agonists in men while functioning as antagonists in women under identical conditions (Barrett, 2006). Molecular gender differences derived from preclinical studies underlie these clinical sexual dimorphisms. The spinal cord cells of male rats express higher levels of μ-opioid receptors in comparison to females, and the depletion of sex hormones produces opposite effects depending on the sex (Kren et al., 2008). In gonadectomized rats, testosterone administration leads to a greater response of β-endorphins in the female compared to the male brain (Pluchino et al., 2009b). Estradiol and progesterone increase levels of both cerebral μ-opioid receptors and circulating β-endorphins (Hammer and Bridges, 1987; Hammer et al., 1993; Pluchino et al., 2009b; Zhou and Hammer, 1995). Correspondingly, the natural selective estrogen receptor modulator (SERM) DT56a enhances β-endorphin levels in the hippocampus, the hypothalamus, the neurointermediate lobe and the anterior pituitary (Pluchino et al., 2009a).

Opioids modulate sex hormone levels in turn. Both clinical and preclinical studies show that acute and chronic administration of opioids for either addiction or chronic pain decreases male and female gonadal hormone levels in plasma and the brain. The

resulting hypogonadism may reach castration level and thus cause common undesirable side effects, such as amenorrhea, galactorrhea, impotency, infertility, loss of libido and potency, fatigue, depression and anxiety (Abs et al., 2000; Aloisi et al., 2009; Ceccarelli et al., 2006; Katz and Mazer, 2009; Rajagopal et al., 2003; Roberts et al., 2002). There are reports of different pathways that may account for the impact of opioids on central and peripheral sex hormones. Morphine activates the 5-α reductase II (SRD5A2) enzyme and therefore enhances the metabolism of testosterone to DHT and 3alpha-diol glucuronide in rat brains (Amini and Ahmadiani, 2005). Moreover, opioids exhibit a direct inhibitory action on the testes and the adrenals, thus causing the peripheral reduction in sex hormone levels (Jenab and Morris, 2000; Pirnik et al., 2001).

The role of the endogenous opioid system in the onset and course of human alcohol dependence has been studied and reviewed extensively, and its role in modulating addictive behavior is firmly established (Kimura and Higuchi, 2011; Kranzler and Edenberg, 2010; Miranda et al., 2010; Oswald and Wand, 2004; Stacey et al., 2009). In particular, increased alcohol intake under stimulation of the endogenous opioid system may be due to an altered palatability of alcohol (Coonfield et al., 2002). However, more general hedonic properties have also been suggested (Kelley et al., 2002). Knockout mouse models for either β-endorphin or μ- or δ-opioid-receptors show altered patterns of alcohol consumption and preference (Grahame et al., 1998; Roberts et al., 2001). The opioid system is already a pharmacological target for the treatment of human alcohol dependence. The opioid antagonist naltrexone reduces the risk for relapse following cessation of drinking (Rösner et al., 2010). This drug is effective, safe and approved for the treatment of alcohol dependence worldwide, including the USA, Europe and Australia. In addition to daily oral application, there are extended-release injectable formulations available in several countries. Opioid antagonists have been shown to eliminate or at least reduce alcohol's reinforcing properties and self-administration in humans (Davidson et al., 1999; O'Malley et al., 1992; Volpicelli et al., 1992) and rats (Davidson and Amit, 1997a,b; Froehlich et al., 1990; Krishnan-Sarin et al., 1995a,b, 1998; Nizhnikov et al., 2006; Stromberg et al., 1998). Moreover, the relationship between the opioid system and alcohol is bidirectional; alcohol intake induces the release of peripheral and mesolimbic β-endorphin and other endogenous opioids, as demonstrated in clinical (Frias et al., 2000, 2002) and preclinical studies (Boyadjieva and Sarkar, 1997; De Waele et al., 1992; De Waele and Gianoulakis, 1993; Olive et al., 2001; Rasmussen et al., 1998).

The interplay between the opioid system, addiction and the HPG axis is further influenced by environmental factors. The alcohol-induced facilitation of social contacts in adolescent rats is mediated by μ-opioid receptor-dependent signaling, either by altered release of endogenous opioids or by changes in receptor sensitivity (Varlinskaya and Spear, 2009). Social interactions *per se* can have rewarding effects (Panksepp and Lahvis, 2007) that contribute to the reinforcing properties of alcohol (Müller and Schumann, 2011). This involves the activation of the mesolimbic DA system and the nucleus accumbens (Gianoulakis, 1996; Herz, 1997). Interestingly, the "social effect" of alcohol gradually declines during the adolescent period (Varlinskaya and Spear, 2002, 2006), reminiscent of the organizational effects of sex hormones. Indeed, the function of the opioid system is affected by the organizational effects of sex hormones. The timing of gonadectomy influences the effects of opioid analgesia in rats (Bodnar and Kest, 2010). Whereas castration of adult female and male rats does not alter their sensitivity to morphine, castration during the early postnatal period shifts the male dose–response curve towards the female curve. Moreover, females masculinized by large doses of testosterone show a dose–response curve similar to that of normal males (Cicero et al., 2002). Given that the organizational effects of sex hormones affect the opioid system, and assuming that the opioid system is involved in the etiopathogenesis of alcohol addiction, these findings support the view of a causal relationship between early sex hormone exposure and development of alcohol dependence.

In summary, both alcohol and testosterone converge in their rewarding effects by modulating opioid signaling in the mesolimbic pathway. Whether those effects are cumulative, complementary, or independent is not completely clear and should be a focus of future research.

5.6. Sex hormones, impulsivity and alcohol intake: a complex and far-reaching interaction

Sex hormones promote the differentiation of behavioral traits like impulsivity. Though the exact categorization is controversial, it includes several sex hormone activity-linked behavioral traits, such as aggression, novelty and sensation seeking and harm avoidance. The multidimensional, psychological construct of impulsivity is an important determinant in alcohol dependence (Lejuez et al., 2010). Because such behaviors are linked to alcohol drinking across cultures (Caspi et al., 1996; Fergusson et al., 1995; Potenza and de Wit, 2010; Pulkkinen and Pitkänen, 1994), they are considered valid risk factors, particularly in boys (Rose, 1998).

The extent of aggressive, novelty-seeking and harm-avoidance behavior is affected by testosterone (Ehrenkranz et al., 1974; Soler et al., 2000). There is evidence of an interaction between activities of sex hormones and cerebral monoamine neurotransmitters in impulsivity. Low levels of the main metabolite of serotonin 5-hydroxyindoleacetic acid (5-HIAA) and high concentrations of testosterone in cerebrospinal fluid were found in alcoholic, impulsive and antisocial offenders (Virkkunen et al., 1994). Functional interplays between testosterone levels, a SNP (rs79874540) coding for a stop codon in the 5-hydroxytryptamine (serotonin) receptor 2B (HTR2B) (Bevilacqua et al., 2010) and a repeat polymorphism in the promoter of the monoamine oxidase A gene (MAOA-LPR) (Sjöberg et al., 2008) have been associated with impulsive and antisocial behavior. In addition, several clinical studies have identified genetic variants within the sex hormone axis that are associated with alcohol addiction-linked personality traits. For instance, the genetics of the ESR1 gene (e.g., the TA polymorphism and the SNP rs722207) and of the AR are related to the extent of harm-avoidance (Gade-Andavolu et al., 2009; Giegling et al., 2009), anxiety (Prichard et al., 2002) and antisocial behavior (Prichard et al., 2007). These results should strongly encourage future studies on genetic variants within the sex hormone axis that are associated with impulsivity and the role of these variants in alcohol dependence.

6. Cellular effects of sex hormone activity and alcohol addiction

The relationship between alcohol dependence and sex is well established. Here, we propose that the sex hormone axis triggers neuroadaptive changes that sensitize the brain to the reinforcing properties of alcohol. Although these aspects have received less attention, the sex hormone axis includes other functionally appreciable units, such as related receptors and the biosynthesis and degradation of sex hormones. Approximately 50% of the variance in human testosterone level can be explained by heritable genetic factors (Hoekstra et al., 2006; Vanbillemont et al., 2010). Interestingly, genetics exerts a stronger influence on the development of alcohol dependence in men than in women (McGue et al., 1992). Against this background, Table 1 was designed to present a partial list of the genes involved in sex hormone activity that may be relevant to alcohol addiction (cf. Fig. 2). More candidate genes may

Table 1
Genes involved in sex hormone activity that may affect alcohol addiction in humans.

Function	Gene		Accession number	Chromosome
Biosynthesis	CYP17A1	Steroid 17-alpha-hydroxylase	NC_000010.10	10q24.3
	CYP19A1	Aromatase	NC_000015.9	15q21.1
	HSD17B1	Hydroxysteroid 17-beta-dehydrogenase 1	NC_000017.10	17q11-q21
	HSD3B2		NC_000001.10	1p13.1
	SRD5A1	3-Oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1	NC_000005.9	5p15
	SRD5A2	3-Oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2	NC_000002.11	2p23
Signaling	AR	Androgen receptor	NC_000023.10	Xq12
	ESR1	Estrogen receptor 1	NC_000006.11	6q25.1
	ESR2	Estrogen receptor 2	NC_000014.8	14q23.2
	PGR	Progesterone receptor	NC_000011.9	11q22-q23
Degradation	CYP1A1		NC_000015.9	15q24.1
	CYP1A2		NC_000015.9	15q24.1
	CYP1B1		NC_000002.11	2p22.2
	GSTM1	Glutathione S-transferase mu 1	NC_000001.10	1p13.3
	GSTP1	Glutathione S-transferase pi 1	NC_000011.9	11q13
	GSTT1	Glutathione S-transferase theta 1	NC_000022.10	22q11.23
	SULT1E1	Sulfotransferase family 1E, estrogen-preferring member	NC_000004.11	4q13.1

be identified using reviews of the sex hormone metabolic pathway (Miller, 2008; Payne and Hales, 2004), the Gene Ontology (GO) database (Ashburner et al., 2000; Gene Ontology Consortium, 2006) and the KEGG database (Aoki and Kanehisa, 2005).

6.1. Human studies

A genome wide association study provides evidence for a link between the rs6902771 SNP of the ESR1 gene and alcohol dependence (Treutlein et al., 2009). In addition, only a small number of hypothesis-driven human studies have been performed on the associations between the genes involved in sex hormone activity and alcohol addiction-related behaviors. However, genetic polymorphisms of the androgen receptor (AR) and the aromatase (CYP19A1) enzyme were shown to be associated with craving for alcohol during withdrawal. The polyglutamine length of the AR is genetically encoded by a CAGn triplet repeat and is related to serum testosterone levels in humans. This association is subject to a sexual dimorphism; the polyglutamine length is correlated positively with serum testosterone levels in males (Crabbe et al., 2007; Krithivas et al., 1999; Travison et al., 2010) and negatively in females (Westberg et al., 2001). This genetic polymorphism is functionally relevant in that the CAGn copy number is negatively correlated with the transcriptional activity of the receptor (Chamberlain et al., 1994; Irvine et al., 2000). Recently, an association between the length of the CAGn AR repeat and alcohol craving during withdrawal has been reported (Lenz et al., 2009). The shorter the polyglutamine tract, the higher the patients scored on the total and obsessive subscales of the obsessive compulsive drinking scale (OCDS). This psychometric instrument quantifies obsession and compulsivity related to craving and drinking behavior, including thoughts of drinking, urges to drink and the ability to resist those thoughts (Anton et al., 1996). This finding is well supported by the previous observations of a link between the CAGn repeat number and testosterone levels (Krithivas et al., 1999; Travison et al., 2010) and by the link between plasma testosterone levels and alcohol withdrawal symptoms (Ruusa and Bergman, 1996). Another mechanism has been suggested to mediate the link between the genetic AR polymorphism and craving. Several authors link appetite-regulating peptides, such as leptin and ghrelin, to the neurobiology of alcohol addiction and especially to cravings for alcohol (Addolorato et al., 2009; Hillemacher et al., 2007; Kiefer et al., 2001a,b, 2005; Leggio, 2010; Wurst et al., 2007). Accordingly, leptin was found to mediate approximately 40% of the observed relationship between the CAGn AR polymorphism and alcohol-craving (Lenz et al., 2010). Leptin is negatively correlated with male serum testosterone levels (Behre et al., 1997) and is positively associated with craving (Hillemacher et al., 2007; Kiefer et al., 2001a,b). This appetite-regulating peptide acts on neurons of the lateral hypothalamus and the VTA. It thereby modulates firing rates of mesolimbic DA neurons (Hommel et al., 2006; Leinninger et al., 2009), the sensitization of which is suggested to underlie the transformation from "wanting" into powerful drug craving (Robinson and Berridge, 1993, 2000). The relationships between the polyglutamine length of the AR, leptin and craving may be useful for clinical decisions in the future, as both leptin and cravings have predictive value for alcohol relapse (Bottlender and Soyka, 2004; Kiefer et al., 2005).

Hillemacher et al. (2009) showed that adipocytokine levels change during alcohol withdrawal. Whereas there is no significant sex difference in adiponectin levels in newborns (Kotani et al., 2004), adult women show higher peripheral levels than men (Sun et al., 2009), suggesting an involvement of the sex hormone axis. However, one study found no contribution of adipocytokines to the relationship between the CAGn AR polymorphism and craving in alcohol-dependent patients (Lenz et al., 2011b).

Alcohol is thought to promote the aromatization of androgens during estrogen biosynthesis (Purohit, 2000). This reaction is catalyzed by aromatase (CYP19A1), which promotes three successive hydroxylations of the A ring of androgens (Fig. 2). Functionally relevant polymorphisms of aromatase are related to peripheral sex hormone levels (Jasienska et al., 2006; Kidokoro et al., 2009). In particular, the higher the number of TTTAn repeats in the exon 4-intron 5 boundary region of the aromatase gene, the lower the testosterone and the higher the estradiol levels in males (Peter et al., 2008). Another report correlated the length of the TTTAn repeat polymorphism and craving during alcohol withdrawal. Patients with longer TTTAn repeats have higher OCDS-compulsive scores (Lenz et al., 2011a). These results further support the modifying role of aromatase in addictive behavior.

Altogether, the above results regarding the associations between alcohol craving, the AR gene and aromatase indicate that sex hormone activity underlies the pathogenesis of alcohol craving. Both the AR and the aromatase enzyme regulate sex hormone levels throughout life, and the genetics of the AR are linked to human leptin levels (Fig. 5). Hence, together with the report of an association between the rs6902771 SNP of the ESR1 gene and alcohol dependence (Treutlein et al., 2009) these findings support our model of the early and continuous activity of sex hormones in alcohol addiction.

Fig. 5. Effects of functional genetic polymorphisms of the AR and aromatase on alcohol craving via modulation of testosterone and leptin levels. AR, androgen receptor.

6.2. Animal studies

There is convincing evidence from basic neuroscience research that the modulation of sex hormone receptors alters cerebral and particularly mesolimbic DA levels, exhibiting reward-related neurochemical effects that cause alcohol addiction-linked behavior. Androgens (Alderson and Baum, 1981; Hernandez et al., 1994) and estrogens (Becker, 1999; Di Paolo et al., 1985; Lammers et al., 1999; Landry et al., 2002; McEwen, 2002) similarly trigger DA responses in the nucleus accumbens and the striatum. This may sensitize the brain to the reinforcing properties of alcohol. In rats, ARs are expressed in the SN and in VTA neurons projecting to the nucleus accumbens (Creutz and Kritzer, 2004; Kritzer, 1997). ESRs are widely expressed in midbrain dopaminergic neurons (Creutz and Kritzer, 2002), in limbic structures and in areas associated with learning and memory (Shughrue et al., 1997). Testosterone and its more potent 5α-reduced metabolite, DHT, cause a down-regulation of the AR in the choroid plexus (Alves et al., 2009) and cerebral cortex in mice. This effect is mediated by sex hormone-induced alterations of DNA methylation in the core promoter region of the AR gene (Kumar and Thakur, 2004). Conversely, testosterone treatments in castrated mice lead to a dose-dependent, linear up-regulation of AR expression in brain areas linked to typical male behavior (i.e., the bed nucleus of the stria terminalis, the medial preoptic area, and the dorsal and ventral aspects of the lateral septum) (Lu et al., 1998). Altogether, the regulation of sex hormone receptors by their ligands appears to be specific to the tissue and age of the rodent investigated (Kerr et al., 1995; Kumar and Thakur, 2004; Turgeon and Waring, 2000).

Blockade of ARs and ESRs reduces the ability of the AAS nandrolone (19-nortestosterone) to modulate the acute reward-related neurochemical effects of amphetamines in rats (Kurling-Kailanto et al., 2010). In mice, winning territorial disputes selectively enhances androgen sensitivity via up-regulation of ARs in the nucleus accumbens and VTA (Fuxjager et al., 2010). These adaptations may directly affect neuroplasticity related to addictive behavior (Kelley, 2004; McBride et al., 1999). In addition, chronic alcohol intake in mature male rats feeds back on ARs and decreases their density in the mediobasal hypothalamus and the adenohypophysis (Babichev et al., 1989).

In summary, both sex hormones and alcohol modulate sex hormone receptor functionality in addiction-related areas of the rodent brain. These effects may initiate critical neuroadaptations that render brain reward systems hypersensitive to alcohol, possibly facilitating the development of alcohol addiction.

7. Handedness and the 2D:4D ratio as peripheral biomarkers of early sex hormone activity in alcohol addiction

The identification of reliable peripheral biomarkers for risk assessment, clinical diagnosis and prognosis of alcohol dependence may be beneficial in developing preventive and therapeutic strategies. Having easy access to these markers would further enhance their practical value. Given the close link between the sex hormone axis and alcohol dependence, biomarkers for sex hormone exposure are interesting in terms of their clinical use. Moreover, markers for sex hormone exposure during different periods in life may enable the identification of developmental periods during which the individual is at increased vulnerability. Early in life, sex hormone exposure is thought to influence handedness and the 2D:4D ratio. These characteristics are easily measurable peripheral markers of cerebral lateralization (Bourne, 2005; Bourne and Gray, 2009; Coulson and Lovett, 2004; Knecht et al., 2000; Proverbio et al., 2006). An abnormal cerebral dominance is linked to several mental disorders, including schizophrenia (Crow, 1997; Klar, 1999; Satz and Green, 1999), autism (Cornish and McManus, 1996; Hauck and Dewey, 2001), depression (Denny, 2009; Hecht, 2010), anxiety, and alcohol dependence (Denny, 2011; Harburg, 1981; London et al., 1985; McNamara et al., 1994; Nasrallah et al., 1983; Sperling et al., 2000, 2010), suggesting a common pathophysiological mechanism.

7.1. The organizational and activational effects of sex hormones on cerebral lateralization

The corpus callosum, which connects the left and right cerebral hemispheres, develops at sex-specific rates in children and adolescents (Luders et al., 2010). The volume of frontal and parietal gray matter reaches its peak 1 year earlier in females than in males, a finding that is in agreement with the earlier age of puberty onset in females (Giedd et al., 1999, 2006, 2009). During adolescence, there is a greater increase of white matter volume in boys than in girls (De Bellis et al., 2001; Lenroot and Giedd, 2006; Lenroot et al., 2007). The human sensitive period for the organizational effects of sex hormones lasts at least until the mid-twenties, when full maturity of the brain is reached (Lenroot and Giedd, 2006). The growth rates in the adolescent brain are linked to the number of CAGn repeats in exon 1 of the AR gene (Perrin et al., 2008). This fact is functionally relevant in that the number of CAGn repeats is inversely proportional to the transcriptional activity of the AR (Chamberlain et al., 1994; Irvine et al., 2000). Perrin et al. (2008) suggested that testosterone activity affects axonal caliber rather than the myelin sheath, possibly by influencing neurofilaments (Hoffman et al., 1987; Marszalek et al., 1996). However, this relationship is not firmly established and more experimental work is required to test the causality between testosterone and increases in brain volume.

Two hypotheses have been proposed to explain the impact of prenatal testosterone on cerebral lateralization. The Geschwind–Behan–Galaburda hypothesis states that high prenatal testosterone interferes with the development of the left hemisphere, thereby favoring the development of the right hemisphere and left-handedness (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985). By contrast, Witelson's callosal hypothesis (Witelson, 1985, 1991; Witelson and Nowakowski, 1991) suggests that there is a link between left-handedness and decreased prenatal testosterone, which may lead to reduced axon elimination, a larger callosal isthmus and functional asymmetry.

In addition to the organizational hypotheses of early testosterone exposure on cerebral lateralization, sex hormones exert activational influences as well. Cerebral dominance varies during the menstrual cycle in females, presumably by regulating interhemispheric spreading of neuronal activation. There is a more bilateral, or at least less asymmetric, cerebral organization during the midluteal phase, which is characterized by high levels of progesterone when compared with levels during menses, which is

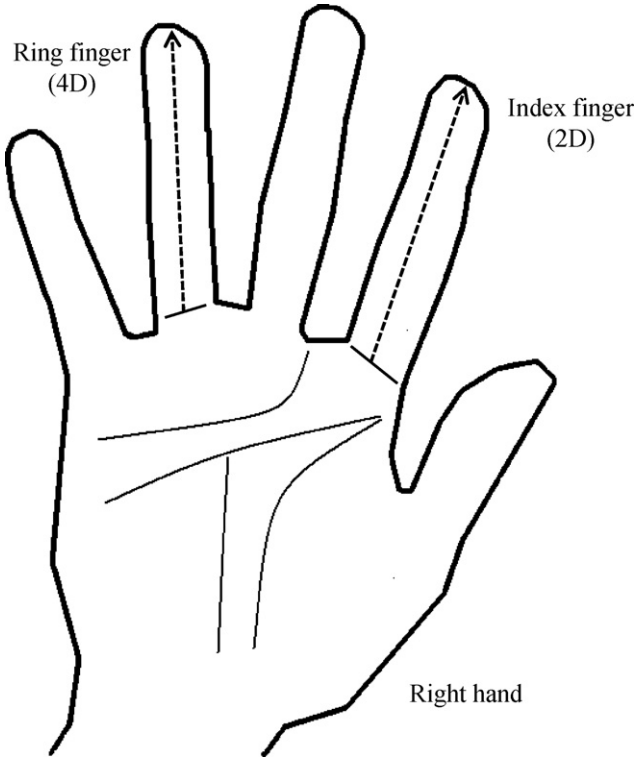

Fig. 6. Illustration of the 2D:4D ratio. The 2D:4D ratio represents the relative length of the index and ring fingers, as demonstrated here on the right hand.

correlated with stronger lateralization patterns. Hemispheric dominance does not differ between normally cycling women during the menses, postmenopausal females and men (Hausmann and Güntürkün, 2000; Hausmann, 2005). In addition, hormone replacement therapy exhibits specific effects on brain asymmetries (Bayer and Erdmann, 2008; Doty et al., 2008).

Taken together, the available evidence strongly suggests an organizational and activational role of sex hormones in human brain development and brain lateralization, influences that act until at least the mid-twenties. Hemispheric dominance is associated with the easily measurable peripheral biomarkers of handedness and the 2D:4D ratio (Fig. 6).

7.2. Handedness and sex hormones

Approximately 90% of humans are right-handed (Gilbert and Wysocki, 1992; Medland et al., 2003; Peters et al., 2006). Although there are a few pathological exceptions, left-handedness is considered a natural phenomenon.

Serum testosterone levels are higher in left-handed subjects (Tan, 1991). Testosterone and estradiol levels correlate negatively with the degree of right-hand preference in right-handed individuals (Tan, 1992). There are higher levels of salivary testosterone in right-handed people of both sexes (Gadea et al., 2003; Moffat and Hampson, 1996). However, recent studies did not detect differences in salivary testosterone levels between left-handed and right-handed individuals (Beaton et al., 2010; Moffat and Hampson, 2000; Vuoksimaa et al., 2010). These controversial results may be due to the differences in the age of the studied cohorts (Vuoksimaa et al., 2010). These results suggest also that handedness represents an organizational rather than an activational effect of sex hormone activity.

To directly investigate the model of early testosterone action in the determination of handedness, sex hormone samples from healthy fetuses would be needed in a longitudinal study. That is hardly feasible. However, an alternative approach to investigate the effect of prenatal testosterone exposure on handedness is to compare females of same-sex twins with females of opposite-sex twins. Although the concept of prenatal testosterone transfer should be applied carefully (Vuoksimaa et al., 2010), it is thought that girls in opposite-sex twin pairs are exposed to elevated testosterone levels prenatally. In line with Witelson's callosal hypothesis, women from opposite-sex twin pairs are more likely to be right-handed (Vuoksimaa et al., 2010), although one study did not find this association (Medland et al., 2009). Another approach is to investigate testosterone levels in newborns. Tan and Tan (2001) reported higher levels of free testosterone in the umbilical cord blood of neonates classified as right-handed according to their grasp reflex.

In summary, prenatal testosterone promotes the development of right-handedness. However, the relationship between handedness and sex hormone levels in adulthood is controversial. These results indicate that the development of handedness reflects organizational rather than activational effects of sex hormone activity.

7.3. Handedness and alcohol addiction

Handedness is implicated in alcohol dependence and addictive behaviors. In a large data set ($n = 27{,}428$) across 12 European countries (mean participant age >50 years), Denny (2011) found a higher frequency of alcohol consumption in left-handed than in right-handed individuals. This result agrees with the majority of studies, which report a higher percentage of left-handedness in patients with alcohol dependence (Harburg, 1981; London et al., 1985; McNamara et al., 1994; Nasrallah et al., 1983), although one investigation (Poikolainen, 2000) failed to detect any relationship. Similarly, a recent study demonstrated that more left-handed or ambidextrous participants developed alcohol addiction than right-handed people (Sperling et al., 2000, 2010). Interestingly, higher levels of testosterone were detected in both non-right-handed male patients and in Lesch type IV patients in this study. Lesch type IV patients are characterized by cerebral damage during brain development and conduct disorder during childhood (Lesch et al., 1988). These findings support our model proposing early effects of sex hormones in alcohol addiction.

The higher prevalence of left-handedness among alcohol dependent patients raises the question of whether prenatal alcohol exposure modulates the handedness of the offspring. Studies on fetal alcohol syndrome (FAS) may partially answer this question. Indeed, children with FAS are more likely to be left-handed than normal children (Domellöf et al., 2009). In addition, prenatally alcohol-exposed individuals show higher rates of delinquency and conduct disorder in later life (Schonfeld et al., 2005) compared with normally developing children. Altogether, it may be concluded that early exposure to testosterone influences the development of handedness, which is associated with alcohol addiction.

7.4. The 2D:4D ratio and early exposure to sex hormones

The 2D:4D ratio is suggested to be a suitable biomarker for prenatal exposure to sex hormones (Fig. 6).

Sex hormone activity affects the early development of the phalangeal anlagen and digit growth via regulation of the HOX genes in embryonic cartilaginous tissue (Forstmeier et al., 2010; McIntyre, 2006). The density of sex hormone receptors is associated with the maturation and growth of the fetal skeleton (Ben-Hur et al., 1997; Zheng and Cohn, 2011). Because the sensitive periods for the influence of sex hormones on growth are specific for each bone, the ratios between the lengths of single digits allow for

the determination of sex hormone exposure during specific developmental periods. As such, the 2D:4D ratio is now widely accepted as a biomarker for prenatal testosterone exposure (Breedlove, 2010; Hönekopp and Watson, 2010; Jackson, 2008; Stoyanov et al., 2009; Zheng and Cohn, 2011; for a critical discussion: Berenbaum et al., 2009; McIntyre, 2006; Wallen, 2009). Multiple lines of evidence support the view that prenatal testosterone exposure reduces the 2D:4D ratio whereas estradiol increases this ratio (Manning et al., 1998). The fetal testosterone/estradiol ratio obtained from amniocentesis is negatively correlated with the 2D:4D ratio 2 years after birth (Lutchmaya et al., 2004). Moreover, the sexual dimorphism of a lower 2D:4D ratio in males is well established by numerous clinical trials (Buck et al., 2003; Jurimäe et al., 2008; Manning et al., 2004, 2007; Nicholls et al., 2008; Robertson et al., 2008; Tan, 2008; Ypsilanti et al., 2008). Twin studies report that women from opposite-sex twin pairs have a lower 2D:4D ratio (van Anders et al., 2006; Voracek and Dressler, 2007) compared with women from same-sex twin pairs. Interestingly, a recent meta-analysis provided persuasive data showing that the 2D:4D ratio is not associated with adult sex hormone levels in the healthy population (Hönekopp et al., 2007). This confirms the validity of the 2D:4D ratio as a reliable biomarker for early sex hormone exposure. In addition, this relationship is corroborated by pathological human conditions. Human adrenal hyperplasia is associated with a lower 2D:4D ratio (Brown et al., 2002; Ökten et al., 2002), whereas the complete androgen insensitivity syndrome is associated with a higher 2D:4D ratio (Berenbaum et al., 2009). There is also direct evidence suggesting a causal relationship between sex hormones and the 2D:4D ratio. Experimentally increased prenatal testosterone levels reduce the 2D:4D ratio in rodents (Talarovicová et al., 2009; Zheng and Cohn, 2011), whereas treatment with estradiol (Zheng and Cohn, 2011) and decreased prenatal testosterone levels following alcohol administration raise the 2D:4D ratio (McMechan et al., 2004). ARs and ESRs appear to mediate these effects, because the deletion of the AR gene increases the 2D:4D ratio and the deletion of the ESR1 gene decreases the 2D:4D ratio in mice (Zheng and Cohn, 2011). Nevertheless, there are some limitations to this approach in humans. The 2D:4D ratio has also been linked to ethnicity (Manning et al., 2000a, 2004) and age in studies of children (McIntyre, 2006). Moreover, the 2D:4D ratio depends on the method used (e.g., photocopies vs. X-rays). Finally, the association between behavior and the 2D:4D ratio may represent pleiotropic genetic effects rather than prenatal testosterone exposure (Section 7.7) (Hurd et al., 2010).

7.5. The 2D:4D ratio and alcohol addiction

Many studies have established a link between the 2D:4D ratio and sex hormone-driven and addiction-linked human behavior. A low 2D:4D ratio predicts reactive aggression in women (Benderlioglu and Nelson, 2004) and is associated with higher physical fitness in teenagers and adults of both sexes (Hönekopp et al., 2006). In addition, women fencers with a lower right hand 2D:4D ratio were shown to be ranked more highly among fencers in the world rankings. The percentage of female left-handers is higher in the fencing sample (21%) than in the general population. Left-handed female fencers had a lower 2D:4D ratio and higher world rankings than those who were right-handed (Bescós et al., 2009). This finding is in agreement with those showing that the 2D:4D ratio of the right hand is lower in left-handed than in right-handed fencers (Voracek et al., 2006). The interaction between the sex hormone axis, handedness, the 2D:4D ratio, athleticism, and aggression/impulsivity raises the question whether the 2D:4D ratio is also connected to alcohol dependence. Indeed, alcohol-dependent men and women have lower 2D:4D ratios and reduced right-left differences (2D:4Dr-l) in comparison to healthy controls (Kornhuber et al., 2011). Because low 2D:4Dr-l values have also been linked to high prenatal testosterone load (Manning, 2002, pp. 21–22), these findings support our early sex hormone activity model of alcohol addiction. Interestingly, this study found no associations between the 2D:4D ratio and the severity of alcohol dependence or craving during withdrawal, suggesting that early testosterone exposure increases the risk for the development of alcohol addiction but does not influence the course of the disease (Kornhuber et al., 2011). The 2D:4D ratio alone is as specific and sensitive as gamma-glutamyl transferase (GGT) activity in diagnosing alcohol dependence (Conigrave et al., 2003). Moreover, high alcohol consumption was correlated with a low 2D:4D ratio in a large non-clinical sample of men and women in the BBC Internet Study ($n = 168{,}748$). National means of alcohol consumed (in liters) per capita per year correlate negatively with the national 2D:4D ratios (Manning and Fink, 2011). These findings provide strong evidence for a link between early sex hormone exposure and the pathogenesis of alcohol addiction and suggest that early testosterone exposure is an independent causal factor (Kornhuber et al., 2011).

Altogether, available evidence suggests that the 2D:4D ratio is a suitable biomarker of early exposure to sex hormones. The reduced 2D:4D ratio in alcohol-dependent patients supports our "critical period" model and indicates that prenatal programming by sex hormones is a crucial mechanism in the development of alcohol dependence. Therefore, the combinatorial effect of exposure to both internal (genetically determined) and external (environmentally determined) sex hormone exposure *in utero* may determine the risk of establishing alcohol addiction throughout life.

7.6. Handedness and the 2D:4D ratio

Findings regarding the relationship between handedness and the 2D:4D ratio have been equivocal. Specifically, a series of studies demonstrated an association between a lower 2D:4D ratio and enhanced left hand performance (Fink et al., 2004; Manning et al., 2000b; Nicholls et al., 2008). In contrast, Ypsilanti et al. (2008) demonstrated that right-handed individuals with intellectual disability of unknown idiopathic origin have a lower 2D:4D ratio in both hands than left-handed people. In addition, a large Internet-based study ($n > 170{,}000$) reported that left-handed individuals have a low 2D:4Dr-l, a low 2D:4D ratio in their right hand and a high 2D:4D ratio in their left hand when compared to the overall average 2D:4D ratio (Manning and Peters, 2009). Another radiographic assessment did not find a relevant association between the 2D:4D ratio and handedness (Robertson et al., 2008). In summary, there are considerable inconsistencies in the literature regarding the relationship between handedness and the 2D:4D ratio (Beaton et al., 2010). Because handedness and the 2D:4D ratio are markers of different stages of human development, a lack of a correlation does not necessarily indicate a theoretical inconsistency (Jackson, 2008). Fig. 7 illustrates the effect of sex hormones on human behavior, alcohol intake, handedness, total digit length and the 2D:4D ratio during different periods of life. Sex hormones influence behavior in a variety of ways throughout one's entire life. Their effects on alcohol drinking behavior become evident during adolescence, which should be understood as a combination of activational and organizational effects (Hibell et al., 2009; Knopik et al., 2004; Young et al., 2002). Prenatal testosterone levels have a major impact on handedness. Although there is a lack of consensus in the literature, postpubertal exposure to testosterone most likely affects handedness as well (Jackson, 2008; Pfannkuche et al., 2009). Total digit length is influenced by prenatal and postnatal sex hormone levels. It correlates moderately with height, sex differences of which become increasingly

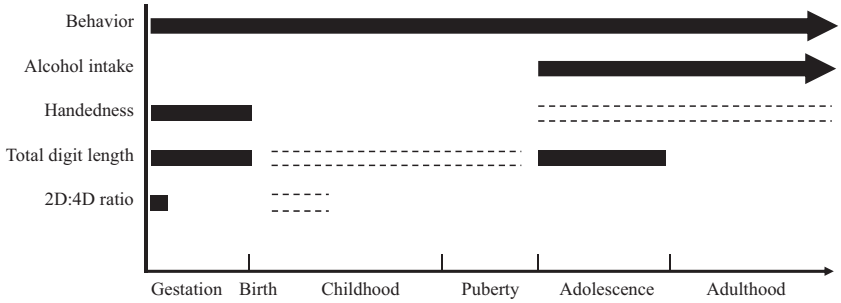

Fig. 7. Influence of sex hormone activity on alcohol drinking and suggested biomarkers for alcohol dependence throughout life. The solid lines represent scientifically accepted periods of the activational and organizational effects of sex hormones. The broken lines represent effects that are not completely understood.

apparent after puberty (Lippa, 2006). Finally, sex hormones influence the 2D:4D ratio *in utero* when the testicles develop and androgen levels increase in male fetuses. The 2D:4D ratio does not change between the 9th week of gestation and birth (Malas et al., 2006). However, there is evidence of an increase in the 2D:4D ratio later in childhood (McIntyre et al., 2005, 2006).

7.7. Cellular effects of sex hormone activity and their relationship to cerebral lateralization, handedness and the 2D:4D ratio

To date, only few human and animal studies have investigated the role of genes related to sex hormone activity in the development of cerebral lateralization, handedness and the 2D:4D ratio.

In gonadally intact male rats and in testosterone-treated females, a higher number of AR-positive CA1 (Cornu Ammonis area 1) cells are found in the left hippocampus than in the right (Xiao and Jordan, 2002). Accordingly, in fetal male rhesus monkeys, AR density differs across cerebral hemispheres; higher expression levels are observed in the left temporal lobe and the right frontal lobe when compared to the contralateral regions. Consistent with the lower degree of lateralization in females, AR density does not vary between the hemispheres in female monkeys (Sholl and Kim, 1990). These findings indicate that interhemispheric differences in AR expression are involved in the development of structural and functional brain lateralization.

Three large twin studies have examined the genetics of handedness. In essence, this research attributes approximately 25% of the variance in adult handedness to additive genetic effects (Medland et al., 2006, 2009; Vuoksimaa et al., 2009). Doyen et al. (2008) reported that 24% of the genetic variance can be explained by the length of the polyglutamine stretch of the AR. CAGn length is positively correlated with testosterone levels in men and negatively correlated in women (Crabbe et al., 2007; Krithivas et al., 1999; Travison et al., 2010; Westberg et al., 2001). Accordingly, left-handedness is related to fewer CAGn repeats in males and more repeats in females (Medland et al., 2005), which is in line with Witelson's hypothesis regarding corpus callosum development.

Twin studies (Medland and Loehlin, 2008; Paul et al., 2006) consistently show that the 2D:4D ratio is highly hereditary (>65% heritability). For this reason, the validity of the ratio as a pure retrospective biomarker of prenatal testosterone exposure was recently questioned (Medland et al., 2010). Hurd et al. (2010) reported that men with fewer CAGn repeats in the AR tend to have higher left-hand 2D:4D ratios compared with men with more CAGn repeats. In contrast, Manning et al. (2003) found that more CAGn repeats are associated with a higher right-hand 2D:4D ratio and a larger difference in 2D:4D ratios between the right and left hands (2D:4Dr-l). Furthermore, the genetics of the ESR1 is linked to the 2D:4D ratio. Approximately 11% of the variation in digit ratio of zebra finches is explained by a polymorphism of the ESR1 (Forstmeier et al., 2010).

In summary, handedness and the 2D:4D ratio represent validated peripheral biomarkers for sex hormone exposure during different periods of human development. Although few studies have been performed with respect to these factors, both metrics are also associated with functional genetic polymorphisms of the sex hormone axis.

7.8. The relationship between handedness, the 2D:4D ratio and alcohol addiction

Sex hormone activity has a lasting organizational effect on the structural development of the human brain. The 2D:4D ratio and handedness are biomarkers for prenatal exposure to sex hormones (Fig. 8). Prenatal exposure to an increased androgen/estrogen ratio causes a low 2D:4D ratio, which is also related to alcohol addiction. However, the significance of handedness is limited because of reports of sex hormone-induced effects after puberty. We speculate that the exposure to an increased androgen/estrogen ratio during early development results in left-handedness, particularly in Lesch type IV alcohol dependent patients, who are characterized by prenatal cerebral impairment (Lesch et al., 1988). Left-handedness is a validated risk factor for alcohol dependence. Therefore, we argue that both handedness and the 2D:4D ratio serve as valid and easily measurable peripheral biomarkers for the organizational cerebral

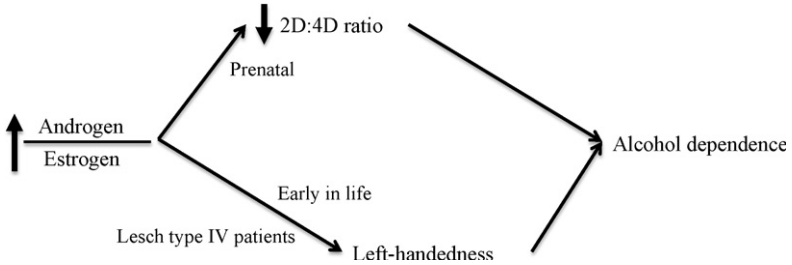

Fig. 8. Handedness and the 2D:4D ratio as peripheral biomarkers of early sex hormone activity and their relationship to alcohol dependence.

effects of sex hormones. These measures are implicated in the reported distinct sex differences in alcohol addiction and affect the brain's sensitivity to the reinforcing properties of alcohol.

8. Potential preventive and therapeutic targets of the sex hormone axis

There is already a considerable number of pharmacological treatment strategies and non-pharmacological associations with preventive and therapeutic potential for the modulation of the sex hormone axis. Among these associations are pre- and perinatal factors, such as antenatal maternal stress (AMS), malnutrition, low birth weight and maternal smoking during pregnancy. Postnatal associations include lifestyle factors, such as drinking green tea, environmental pollution, partnership status, age, body mass index (BMI), abdominal fat, muscle strength, smoking, sleep and physical activity. Hence, further clarifying the causal role of sex hormone activity in the etiopathogenesis of alcohol dependence may allow the development of preventive and therapeutic strategies in the near future.

8.1. Pharmacological targets

Pharmacological targets exist at all levels of the sex hormone axis. There are already many substances in clinical use that modulate the signaling of androgens, estrogens and gestagens. These include synthetic steroids and anti-steroids that either activate or block steroid receptors or modulate the enzymes relevant for the metabolism of sex hormones, such as aromatase or SRD5A2. In spite of the great number of these sex hormone modulators, there are few published studies on the effects of these compounds on alcohol-associated disorders. In humans, the SRD5A2 inhibitor finasteride attenuates subjective responses to self-administered alcohol in moderate drinkers (Pierucci-Lagha et al., 2005). In male mice, the intraperitoneal injection of finasteride decreases voluntary alcohol intake and prevents the development of alcohol preference (Ford et al., 2005, 2008). Moreover, the LH-releasing hormone agonist leuprolide attenuates the expression and development of alcohol dependence and sensitization in male mice (Umathe et al., 2008). The SERM toremifene was shown to be partially protective against alcohol-induced liver lesions in female rats (Järveläinen et al., 2001). Astonishingly, to the best of our knowledge, there are currently no clinical studies available that investigate the potential benefit of pharmaceuticals that interfere with the sex hormone axis in patients suffering from alcohol dependence. However, once we better understand the components of the sex hormone axis that underlie the pathogenesis of alcohol dependence, there will be the need to test these substances for their benefit in the prevention and treatment of alcohol dependence and related addictive behaviors.

8.2. Antenatal maternal stress, nutrition and smoking behavior

Results from clinical and preclinical studies indicate that AMS, malnutrition and smoking behavior contribute to the development of alcohol addiction in later life. A clinical study on pregnant women reports a correlation between amniotic fluid levels of cortisol and testosterone. This finding suggests a link between AMS and increased prenatal testosterone exposure (Sarkar et al., 2008). The idea that AMS contributes to the development of alcohol addiction in adulthood via modulation of prenatal sex hormone exposure is supported by a number of experimental studies. In rodents, AMS shapes behavioral and biological profiles of the offspring. It causes behavioral masculinization with increased circulating testosterone levels in the female offspring and behavioral infantilization in the male offspring. Accordingly, AMS entails sex-specific alterations of AR and ESR1 expression in the CNS (medial preoptic area, nucleus arcuatus of the hypothalamus, CA1 region of the hippocampus) (Sachser et al., 2011). Interestingly, a recent investigation revealed an association between AMS and a reduced 2D:4D ratio of the offspring (Lilley et al., 2010). In line with our early sex hormone activity model of alcohol addiction, AMS affects the brain reward system and results in a higher operant responding and alcohol intake during alcohol reinforcement (Campbell et al., 2009). Moreover, prenatal stress also modulates behavioral (locomotor reactivity to novelty) and pharmacological (induction of ΔFosB in the nucleus accumbens) effects of alcohol (Van Waes et al., 2011).

Maternal malnutrition causes low birth weight of the offspring (Martorell and González-Cossío, 1987), a factor that has been shown to be related to reduced testosterone concentrations in preterm newborns born small for gestational age (Scaramuzzo et al., 2010) and in adults (Vanbillemont et al., 2010). Unexpectedly, this relationship is not found in adolescents (Boonstra et al., 2008; Kerkhof et al., 2009). The investigation of individuals born during the Dutch Hunger Winter (1944–1945) at the end of World War II gives insight into the role of perinatal malnutrition and pathologies in later life. The exposure to famine before birth and during the early neonatal period is a risk factor for an array of diverse disorders in adulthood, such as early onset coronary artery disease (Painter et al., 2006b), breast cancer (Painter et al., 2006a), congenital anomalies of the central nervous system (Susser et al., 1998), impaired cognitive function (de Rooij et al., 2010), schizophrenia spectrum disorders (Hoek et al., 1998), alcohol dependence and drug abuse (Franzek et al., 2008). The observation that exposure to hunger during the first trimester is associated with addiction of males in later life (Franzek et al., 2008) is in line with our early sex hormone activity model of alcohol dependence. Moreover, maternal smoking behavior during pregnancy causes low birth weight and fetal growth restriction (Vardavas et al., 2010), altering the sex hormone axis of the offspring (Ramlau-Hansen et al., 2008). We therefore consider AMS, malnutrition, birth weight and smoking behavior as potential preventive and therapeutic targets to address alcohol addiction in adulthood. However, our model does not posit that the development of alcohol dependence follows an all-or-none principle. In rats, social experiences may restore or at least ameliorate the behavioral deficits that arise due to the lack of sex hormones during early development. This effect indicates that the social context influences the same neural pathways and mechanisms as do sex hormones (Schulz et al., 2009a). Moreover, differences in addictive behavior that are associated with sexual maturation disappear when risky behaviors become more common in the adolescent peer group (Bratberg et al., 2005; Dick et al., 2000).

8.3. Lifestyle factors

Green tea is thought to be protective against breast cancer, possibly due to its effects on sex hormone signaling (Sartippour et al., 2006; Shrubsole et al., 2009; Wu and Butler, 2011; Zhang et al., 2009). Its consumption is associated with reduced peripheral estrogen levels in Asian women (Nagata et al., 1998; Wu et al., 2005). Green tea contains diverse phytochemical compounds, particularly catechins that influence different biological mechanisms, including the sex hormone axis. The most abundant catechin in green tea is the polyphenol epigallocatechin gallate (EGCG). It modulates enzymes relevant for the synthesis and degradation of estradiol, e.g., the inhibition of aromatase and cytosolic catechol-O-methyltransferase (COMT) in the human liver (Goodin and Rosengren, 2003; Nagai et al., 2004; Satoh et al., 2002). In addition, *in vitro* studies show that EGCG down regulates ER function in breast cancer cells (Farabegoli et al., 2007) and AR expression in a prostate cancer cell line (Ren et al., 2000).

There are other, presumably causal factors that have been shown to be associated with sex hormone levels in humans, such as environmental pollution, being "in love", partnership, marital status, age, BMI, sleep quality and physical activity. Accordingly, there is evidence that the exposure to endocrine-disrupting chemicals that are generated by environmental pollution (e.g., hexochlorobenzene, polychlorinated biphenyls) affect sex hormone function, causing an earlier onset of puberty and an elevated male/female ratio in human adolescents (Croes et al., 2009; Den Hond et al., 2011) and zebrafish (Lyche et al., 2011). Moreover, "falling in love" is associated with reduced testosterone concentrations in men and increased levels in women (Marazziti and Canale, 2004). Singles have higher peripheral testosterone levels than monoamorously partnered women and men (van Anders and Watson, 2006; van Anders and Goldey, 2010). In contrast, being married is related to lower total and bioavailable testosterone (Atlantis et al., 2009). Interestingly, data derived from experiments in rats suggest that the reinforcing effects of sexual behavior may be equally strong as those of alcohol (Pfaus et al., 2010). Furthermore, a younger age, a low BMI, low abdominal fat, low triglycerides, low muscle strength, smoking, high-intensity exercise and long duration of sleep are linked to higher levels of total peripheral and bioavailable testosterone in middle-aged healthy men (Atlantis et al., 2009; Barrett-Connor et al., 2008; Goh et al., 2007; Goh and Tong, 2011; Hall et al., 2008; Suzuki et al., 2009; Travison et al., 2007; Wu et al., 2008). In women, physical activity was found to be associated with lower levels of 17β-estradiol (Emaus et al., 2008). With respect to the impact of sex hormones on cancer development and rate of tumor growth, the discussed relationship between physical activity and sex hormones corresponds to the beneficial effects of physical exercise on the risk for colon, breast and endometrial cancers (Bernstein, 2008; Friedenreich et al., 2010; McTiernan, 2008). Interestingly, age as a risk factor may be overcome by a healthier lifestyle (Yeap et al., 2009). A recent Cochrane Review demonstrated that the combination of dietary, exercise and behavioral interventions is effective in the treatment of hyperandrogenism (such as high testosterone) in females suffering from polycystic ovary syndrome (Moran et al., 2011), suggestive of a causal relationship. Hence, if one accepts the relationships between lifestyle and sex hormones as causal, one should consider a systematic change in lifestyle as a potential strategy to modulate the sex hormone axis for the prevention and treatment of alcohol addiction.

9. Summary, conclusions and perspectives

Alcohol-associated disorders are among the leading preventable causes of death across the globe. The aim of this review is to outline the current knowledge on the relationship between the activational and organizational effects of the sex hormone axis and alcohol dependence. The relevance of the topic is illustrated by a vast number of basic science and applied research studies. There are definite sex differences in the prevalence, onset and course of alcohol addiction. Differences are also found in alcohol drinking behaviors, the physiological and behavioral consequences of alcohol use, the degradation of alcohol, its reinforcing properties and the underlying intra- and intercellular molecular pathways. Moreover, pathological alcohol consumption begins during adolescence, a period characterized by distinct, sex hormone-driven neurodevelopmental changes.

Sex hormone activity is not limited to sex hormones *per se* but must be extended to include the HPG axis, the biosynthesis and degradation of androgens and estrogens, and their down-stream signaling effects. The intricate, functional interactions between different sex hormones and their interactions with the HPA axis and the opioid system add further levels of complexity to the prediction of how endocrinological profiles shape alcohol addiction-related behaviors.

The relationship between the sex hormone axis and alcohol drinking behavior is bidirectional. Consistent with the definition of activational effects, sex hormone activity modulates alcohol-associated addictive behaviors, such as craving, preference and drinking. Intriguingly, the effects of single sex hormones on addictive behaviors differ between the genders. The clinical phenomenon of AAS dependence may be cited as direct evidence for the modulating capacity of sex hormones in human addictive disorders. Acute and chronic alcohol consumption feed back on sex hormone activity with subsequent changes in alcohol drinking behavior. This indicates that the role of the sex hormone axis in alcohol dependence may shift during the course of the disease. However, this idea warrants further investigation of sex hormone activity during different stages of alcohol dependence.

There would be a great benefit in the identification of reliable and easily quantifiable biomarkers for the clinical diagnosis and prognosis of alcohol dependence. Left-handedness and a low 2D:4D ratio are associated with alcohol addiction. These peripheral biomarkers vary in their sensitive window for sex hormone exposure and thus represent different stages of human development. We speculate that the organizational effects of sex hormones trigger neuroadaptive changes that sensitize the brain's reward system to the reinforcing properties of alcohol, thereby predisposing an individual to alcohol addiction. In particular, prenatal programming by sex hormones may represent a crucial mechanism in the development of alcohol dependence. The combination of exposure to internal (genetically determined) and external (environmentally determined) sex hormones *in utero* and during early development contributes to the risk of establishing alcohol addiction later in life. Furthermore, this model also implies that the sensitive period to both organizational and activational effects of sex hormones continues throughout one's lifetime.

Our understanding of the sex hormone activity-related mechanisms that underlie the development and course of alcohol dependence is incomplete; several controversial findings on sex hormones and alcohol addiction require additional investigation. Future studies, particularly on the role of the biosynthesis, signaling and degradation of sex hormones are needed. Also required are analyses into peripheral biomarkers of lifetime sex hormone activity. Studies should be more specific given the high phenomenological heterogeneity of alcohol-dependent patients. Moreover, it is clear from the fact that findings from male-only studies cannot be easily applied to females that investigations of alcohol addiction must be performed separately for males and females. Studies of females should in turn more carefully consider confounding variables, such as the use of oral contraceptives, hormone therapy, pre- and postmenopausal status and the physiological and alcohol-induced pathological changes of sex hormone activity during the menstrual cycle.

Several pharmacological and potential non-pharmacological targets for the modulation of the sex hormone axis are available, such as AMS, prenatal malnutrition, low birth weight, and maternal smoking during pregnancy. Other factors include lifestyle characteristics, such as green tea consumption, environmental pollution, BMI, muscle strength, physical activity and smoking behavior. Thus, the clarification of the causal role of sex hormone activity in the etiopathogenesis of alcohol dependence may entail preventive and therapeutic strategies in the near future.

Role of funding source

Funding was provided by the Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany.

Conflict of interest

None of the authors had a financial or personal conflict of interest.

Acknowledgment

We thank the reviewers for constructive suggestions.

References

Abs, R., Verhelst, J., Maeyaert, J., Van Buyten, J.P., Opsomer, F., Adriaensen, H., Verlooy, J., Van Havenbergh, T., Smet, M., Van Acker, K., 2000. Endocrine consequences of long-term intrathecal administration of opioids. J. Clin. Endocrinol. Metab. 85, 2215–2222.

Adams, M.L., Forman, J.B., Kalicki, J.M., Meyer, E.R., Sewing, B., Cicero, T.J., 1993. Antagonism of alcohol-induced suppression of rat testosterone secretion by an inhibitor of nitric oxide synthase. Alcohol. Clin. Exp. Res. 17, 660–664.

Addolorato, G., Leggio, L., Hillemacher, T., Kraus, T., Jerlhag, E., Bleich, S., 2009. Hormones and drinking behaviour: new findings on ghrelin, insulin, leptin and volume-regulating hormones. An ESBRA Symposium report. Drug Alcohol Rev. 28, 160–165.

Ahlbom, E., Prins, G.S., Ceccatelli, S., 2001. Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. Brain Res. 892, 255–262.

Alderson, L.M., Baum, M.J., 1981. Differential effects of gonadal steroids on dopamine metabolism in mesolimbic and nigro-striatal pathways of male rat brain. Brain Res. 218, 189–206.

Almeida, O.F., Shoaib, M., Deicke, J., Fischer, D., Darwish, M.H., Patchev, V.K., 1998. Gender differences in ethanol preference and ingestion in rats. The role of the gonadal steroid environment. J. Clin. Invest. 101, 2677–2685.

Aloisi, A.M., Aurilio, C., Bachiocco, V., Biasi, G., Fiorenzani, P., Pace, M.C., Paci, V., Pari, G., Passavanti, G., Ravaioli, L., Sindaco, G., Vellucci, R., Ceccarelli, I., 2009. Endocrine consequences of opioid therapy. Psychoneuroendocrinology 34 (Suppl. 1), S162–S168.

Alomary, A.A., Vallee, M., O'Dell, L.E., Koob, G.F., Purdy, R.H., Fitzgerald, R.L., 2003. Acutely administered ethanol participates in testosterone synthesis and increases testosterone in rat brain. Alcohol. Clin. Exp. Res. 27, 38–43.

Alves, C.H., Gonçalves, I., Socorro, S., Baltazar, G., Quintela, T., Santos, C.R.A., 2009. Androgen receptor is expressed in murine choroid plexus and downregulated by 5alpha-dihydrotestosterone in male and female mice. J. Mol. Neurosci. 38, 41–49.

Amini, H., Ahmadiani, A., 2005. In vivo evidence for an increase in 5alpha-reductase activity in the rat central nervous system following morphine exposure. Int. J. Dev. Neurosci. 23, 621–626.

Anton, R.F., Moak, D.H., Latham, P.K., 1996. The obsessive compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. Arch. Gen. Psychiatry 53, 225–231.

Aoki, K.F., Kanehisa, M., 2005. Using the KEGG database resource. Curr. Protoc. Bioinformatics Chapter 1, Unit 1 12.

Apter, S.J., Eriksson, C.J.P., 2003. The effect of alcohol on testosterone concentrations in alcohol-preferring and non-preferring rat lines. Alcohol. Clin. Exp. Res. 27, 1190–1193.

Apter, S.J., Eriksson, C.J.P., 2006. The role of social isolation in the effects of alcohol on corticosterone and testosterone levels of alcohol-preferring and non-preferring rats. Alcohol Alcohol. 41, 33–38.

Archer, J., 1991. The influence of testosterone on human aggression. Br. J. Psychol. 82 (Pt. 1), 1–28.

Arnold, A.P., 2009. The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm. Behav. 55, 570–578.

Arnold, A.P., Breedlove, S.M., 1985. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. Horm. Behav. 19, 469–498.

Arvary, D., Pope Jr., H.G., 2000. Anabolic-androgenic steroids as a gateway to opioid dependence. N. Engl. J. Med. 342, 1532.

Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., Harris, M.A., Hill, D.P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J.C., Richardson, J.E., Ringwald, M., Rubin, G.M., Sherlock, G., 2000. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat. Genet. 25, 25–29.

Atlantis, E., Martin, S.A., Haren, M.T., O'Loughlin, P.D., Taylor, A.W., Anand-Ivell, R., Ivell, R., Wittert, G.A., 2009. Demographic, physical and lifestyle factors associated with androgen status: the Florey Adelaide Male Ageing Study (FAMAS). Clin. Endocrinol. (Oxf.) 71, 261–272.

Babichev, V.N., Peryshkova, T.A., Avazashvili, N.I., Shishkina, I.V., 1989. Effect of alcohol on the content of sex steroid receptors in the hypothalamus and hypophysis of male rats. Biull. Eksp. Biol. Med. 107, 204–207.

Babor, T.F., Hofmann, M., DelBoca, F.K., Hesselbrock, V., Meyer, R.E., Dolinsky, Z.S., Rounsaville, B., 1992. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch. Gen. Psychiatry 49, 599–608.

Barrett-Connor, E., Dam, T.T., Stone, K., Harrison, S.L., Redline, S., Orwoll, E., 2008. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. J. Clin. Endocrinol. Metab. 93, 2602–2609.

Barrett, A.C., 2006. Low efficacy opioids: implications for sex differences in opioid antinociception. Exp. Clin. Psychopharmacol. 14, 1–11.

Baum, M.J., 1979. Differentiation of coital behavior in mammals: a comparative analysis. Neurosci. Biobehav. Rev. 3, 265–284.

Bayer, U., Erdmann, G., 2008. The influence of sex hormones on functional cerebral asymmetries in postmenopausal women. Brain Cogn. 67, 140–149.

Beaton, A.A., Rudling, N., Kissling, C., Taurines, R., Thome, J., 2010. Digit ratio (2D:4D), salivary testosterone, and handedness. Laterality 1–20.

Beck, K.H., Treiman, K.A., 1996. The relationship of social context of drinking, perceived social norms, and parental influence to various drinking patterns of adolescents. Addict. Behav. 21, 633–644.

Becker, J.B., 1999. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol. Biochem. Behav. 64, 803–812.

Becker, J.B., Hu, M., 2008. Sex differences in drug abuse. Front. Neuroendocrinol. 29, 36–47.

Behre, H.M., Simoni, M., Nieschlag, E., 1997. Strong association between serum levels of leptin and testosterone in men. Clin. Endocrinol. (Oxf.) 47, 237–240.

Belin, D., Everitt, B.J., 2008. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron 57, 432–441.

Belin, D., Jonkman, S., Dickinson, A., Robbins, T.W., Everitt, B.J., 2009. Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. Behav. Brain Res. 199, 89–102.

Bell, R.L., Rodd, Z.A., Sable, H.J.K., Schultz, J.A., Hsu, C.C., Lumeng, L., Murphy, J.M., McBride, W.J., 2006. Daily patterns of ethanol drinking in peri-adolescent and adult alcohol-preferring (P) rats. Pharmacol. Biochem. Behav. 83, 35–46.

Ben-Hur, H., Thole, H.H., Mashiah, A., Insler, V., Berman, V., Shezen, E., Elias, D., Zuckerman, A., Ornoy, A., 1997. Estrogen, progesterone and testosterone receptors in human fetal cartilaginous tissue: immunohistochemical studies. Calcif. Tissue Int. 60, 520–526.

Benderlioglu, Z., Nelson, R.J., 2004. Digit length ratios predict reactive aggression in women, but not in men. Horm. Behav. 46, 558–564.

Bennett, N.C., Gardiner, R.A., Hooper, J.D., Johnson, D.W., Gobe, G.C., 2010. Molecular cell biology of androgen receptor signalling. Int. J. Biochem. Cell Biol. 42, 813–827.

Berenbaum, S.A., Bryk, K.K., Nowak, N., Quigley, C.A., Moffat, S., 2009. Fingers as a marker of prenatal androgen exposure. Endocrinology 150, 5119–5124.

Berner, P., Lesch, O.M., Walter, H., 1986. Alcohol and depression. Psychopathology 19 (Suppl. 2), 177–183.

Bernstein, L., 2008. Identifying population-based approaches to lower breast cancer risk. Oncogene 27 (Suppl. 2), S3–S8.

Berridge, K.C., Ho, C.Y., Richard, J.M., DiFeliceantonio, A.G., 2010. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res. 1350, 43–64.

Bescós, R., Esteve, M., Porta, J., Mateu, M., Irurtia, A., Voracek, M., 2009. Prenatal programming of sporting success: associations of digit ratio (2D:4D), a putative marker for prenatal androgen action, with world rankings in female fencers. J. Sports Sci. 27, 625–632.

Bevilacqua, L., Doly, S., Kaprio, J., Yuan, Q., Tikkanen, R., Paunio, T., Zhou, Z., Wedenoja, J., Maroteaux, L., Diaz, S., Belmer, A., Hodgkinson, C.A., Dell'osso, L., Suvisaari, J., Coccaro, E., Rose, R.J., Peltonen, L., Virkkunen, M., Goldman, D., 2010. A population-specific HTR2B stop codon predisposes to severe impulsivity. Nature 468, 1061–1066.

Beyenburg, S., Watzka, M., Clusmann, H., Blümcke, I., Bidlingmaier, F., Elger, C.E., Stoffel-Wagner, B., 2000. Androgen receptor mRNA expression in the human hippocampus. Neurosci. Lett. 294, 25–28.

Blanchard, B.A., Glick, S.D., 1995. Sex differences in mesolimbic dopamine responses to ethanol and relationship to ethanol intake in rats. Recent Dev. Alcohol. 12, 231–241.

Blanchard, B.A., Steindorf, S., Wang, S., Glick, S.D., 1993. Sex differences in ethanol-induced dopamine release in nucleus accumbens and in ethanol consumption in rats. Alcohol. Clin. Exp. Res. 17, 968–973.

Bodnar, R.J., Kest, B., 2010. Sex differences in opioid analgesia, hyperalgesia, tolerance and withdrawal: central mechanisms of action and roles of gonadal hormones. Horm. Behav. 58, 72–81.

Boileau, I., Assaad, J.M., Pihl, R.O., Benkelfat, C., Leyton, M., Diksic, M., Tremblay, R.E., Dagher, A., 2003. Alcohol promotes dopamine release in the human nucleus accumbens. Synapse 49, 226–231.

Boonstra, V.H., Weber, R.F.A., de Jong, F.H., Hokken-Koelega, A.C.S., 2008. Testis function in prepubertal boys and young men born small for gestational age. Horm. Res. 70, 357–363.

Bottlender, M., Soyka, M., 2004. Impact of craving on alcohol relapse during, and 12 months following, outpatient treatment. Alcohol Alcohol. 39, 357–361.

Boulware, M.I., Mermelstein, P.G., 2009. Membrane estrogen receptors activate metabotropic glutamate receptors to influence nervous system physiology. Steroids 74, 608–613.

Bourne, V.J., 2005. Lateralised processing of positive facial emotion: sex differences in strength of hemispheric dominance. Neuropsychologia 43, 953–956.

Bourne, V.J., Gray, D.L., 2009. Hormone exposure and functional lateralisation: examining the contributions of prenatal and later life hormonal exposure. Psychoneuroendocrinology 34, 1214–1221.

Boyadjieva, N.I., Sarkar, D.K., 1997. Effects of ethanol on basal and prostaglandin E1-induced increases in beta-endorphin release and intracellular cAMP levels in hypothalamic cells. Alcohol. Clin. Exp. Res. 21, 1005–1009.

Bratberg, G.H., Nilsen, T.I.L., Holmen, T.L., Vatten, L.J., 2005. Sexual maturation in early adolescence and alcohol drinking and cigarette smoking in late adolescence: a prospective study of 2,129 Norwegian girls and boys. Eur. J. Pediatr. 164, 621–625.
Breedlove, S.M., 2010. Minireview: organizational hypothesis: instances of the fingerpost. Endocrinology 151, 4116–4122.
Brower, K.J., Blow, F.C., Young, J.P., Hill, E.M., 1991. Symptoms and correlates of anabolic-androgenic steroid dependence. Br. J. Addict. 86, 759–768.
Brown, W.M., Hines, M., Fane, B.A., Breedlove, S.M., 2002. Masculinized finger length patterns in human males and females with congenital adrenal hyperplasia. Horm. Behav. 42, 380–386.
Bruchovsky, N., Wilson, J.D., 1968. The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. J. Biol. Chem. 243, 2012–2021.
Brunell, S.C., Spear, L.P., 2005. Effect of stress on the voluntary intake of a sweetened ethanol solution in pair-housed adolescent and adult rats. Alcohol. Clin. Exp. Res. 29, 1641–1653.
Buck, J.J., Williams, R.M., Hughes, I.A., Acerini, C.L., 2003. In-utero androgen exposure and 2nd to 4th digit length ratio-comparisons between healthy controls and females with classical congenital adrenal hyperplasia. Hum. Reprod. 18, 976–979.
Buydens-Branchey, L., Branchey, M.H., Noumair, D., 1989. Age of alcoholism onset. I. Relationship to psychopathology. Arch. Gen. Psychiatry 46, 225–230.
Cailhol, S., Mormède, P., 2001. Sex and strain differences in ethanol drinking: effects of gonadectomy. Alcohol. Clin. Exp. Res. 25, 594–599.
Campbell, J.C., Szumlinski, K.K., Kippin, T.E., 2009. Contribution of early environmental stress to alcoholism vulnerability. Alcohol 43, 547–554.
Carruthers, M., 2008. The paradox dividing testosterone deficiency symptoms and androgen assays: a closer look at the cellular and molecular mechanisms of androgen action. J. Sex Med. 5, 998–1012.
Caspi, A., Moffitt, T.E., Newman, D.L., Silva, P.A., 1996. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. Arch. Gen. Psychiatry 53, 1033–1039.
Castilla-García, A., Santolaria-Fernández, F.J., González-Reimers, C.E., Batista-López, N., González-García, C., Jorge-Hernández, J.A., Hernández-Nieto, L., 1987. Alcohol-induced hypogonadism: reversal after ethanol withdrawal. Drug Alcohol Depend. 20, 255–260.
Ceccarelli, I., De Padova, A.M., Fiorenzani, P., Massafra, C., Aloisi, A.M., 2006. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. Neuroscience 140, 929–937.
Ceylan-Isik, A.F., McBride, S.M., Ren, J., 2010. Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? Life Sci. 87, 133–138.
Chamberlain, N.L., Driver, E.D., Miesfeld, R.L., 1994. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. 22, 3181–3186.
Chambers, R.A., Taylor, J.R., Potenza, M.N., 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am. J. Psychiatry 160, 1041–1052.
Chester, J.A., Barrenha, G.D., Hughes, M.L., Keuneke, K.J., 2008. Age- and sex-dependent effects of footshock stress on subsequent alcohol drinking and acoustic startle behavior in mice selectively bred for high-alcohol preference. Alcohol. Clin. Exp. Res. 32, 1782–1794.
Chia, Y.Y., Chow, L.H., Hung, C.C., Liu, K., Ger, L.P., Wang, P.N., 2002. Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients. Can. J. Anaesth. 49, 249–255.
Chrostek, L., Jelski, W., Szmitkowski, M., Puchalski, Z., 2003. Gender-related differences in hepatic activity of alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in humans. J. Clin. Lab. Anal. 17, 93–96.
Cicero, T.J., Adams, M.L., O'Connor, L.H., Nock, B., 1989. In vivo evidence for a direct effect of naloxone on testicular steroidogenesis in the male rat. Endocrinology 125, 957–963.
Cicero, T.J., Badger, T.M., 1977. Effects of alcohol on the hypothalamic-pituitary-gonadal axis in the male rat. J. Pharmacol. Exp. Ther. 201, 427–433.
Cicero, T.J., Nock, B., O'Connor, L., Meyer, E.R., 2002. Role of steroids in sex differences in morphine-induced analgesia: activational and organizational effects. J. Pharmacol. Exp. Ther. 300, 695–701.
Cloninger, C.R., 1987. Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.
Cloninger, C.R., Bohman, M., Sigvardsson, S., 1981. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch. Gen. Psychiatry 38, 861–868.
Conigrave, K.M., Davies, P., Haber, P., Whitfield, J.B., 2003. Traditional markers of excessive alcohol use. Addiction 98 (Suppl. 2), 31–43.
Contarino, A., Picetti, R., Matthes, H.W., Koob, G.F., Kieffer, B.L., Gold, L.H., 2002. Lack of reward and locomotor stimulation induced by heroin in mu-opioid receptor-deficient mice. Eur. J. Pharmacol. 446, 103–109.
Coonfield, D.L., Hill, K.G., Kaczmarek, H.J., Ferraro 3rd, F.M., Kiefer, S.W., 2002. Low doses of naltrexone reduce palatability and consumption of ethanol in outbred rats. Alcohol 26, 43–47.
Cornish, K.M., McManus, I.C., 1996. Hand preference and hand skill in children with autism. J. Autism Dev. Disord. 26, 597–609.
Coulson, S., Lovett, C., 2004. Handedness, hemispheric asymmetries, and joke comprehension. Brain Res. Cogn. Brain Res. 19, 275–288.
Crabbe, P., Bogaert, V., De Bacquer, D., Goemaere, S., Zmierczak, H., Kaufman, J.M., 2007. Part of the interindividual variation in serum testosterone levels in healthy men reflects differences in androgen sensitivity and feedback set point: contribution of the androgen receptor polyglutamine tract polymorphism. J. Clin. Endocrinol. Metab. 92, 3604–3610.
Creutz, L.M., Kritzer, M.F., 2002. Estrogen receptor-beta immunoreactivity in the midbrain of adult rats: regional, subregional, and cellular localization in the A10, A9, and A8 dopamine cell groups. J. Comp. Neurol. 446, 288–300.
Creutz, L.M., Kritzer, M.F., 2004. Mesostriatal and mesolimbic projections of midbrain neurons immunoreactive for estrogen receptor beta or androgen receptors in rats. J. Comp. Neurol. 476, 348–362.
Croes, K., Baeyens, W., Bruckers, L., Den Hond, E., Koppen, G., Nelen, V., Van de Mieroop, E., Keune, H., Dhooge, W., Schoeters, G., Van Larebeke, N., 2009. Hormone levels and sexual development in Flemish adolescents residing in areas differing in pollution pressure. Int. J. Hyg. Environ. Health 212, 612–625.
Crow, T.J., 1997. Schizophrenia as failure of hemispheric dominance for language. Trends Neurosci. 20, 339–343.
Dabbs Jr., J.M., 1990a. Age and seasonal variation in serum testosterone concentration among men. Chronobiol. Int. 7, 245–249.
Dabbs Jr., J.M., 1990b. Salivary testosterone measurements: reliability across hours, days, and weeks. Physiol. Behav. 48, 83–86.
Dabbs Jr., J.M., Morris, R., 1990. Testosterone, social class, and antisocial behavior in a sample of 4,462 men. Psychol. Sci. 1, 209–211.
Dalley, J.W., Everitt, B.J., 2009. Dopamine receptors in the learning, memory and drug reward circuitry. Semin. Cell Dev. Biol. 20, 403–410.
Davidson, D., Amit, Z., 1997a. Effect of ethanol drinking and naltrexone on subsequent drinking in rats. Alcohol 14, 581–584.
Davidson, D., Amit, Z., 1997b. Naltrexone blocks acquisition of voluntary ethanol intake in rats. Alcohol. Clin. Exp. Res. 21, 677–683.
Davidson, D., Palfai, T., Bird, C., Swift, R., 1999. Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol. Clin. Exp. Res. 23, 195–203.
De Bellis, M.D., Keshavan, M.S., Beers, S.R., Hall, J., Frustaci, K., Masalehdan, A., Noll, J., Boring, A.M., 2001. Sex differences in brain maturation during childhood and adolescence. Cereb. Cortex 11, 552–557.
de Jonge, F.H., Muntjewerff, J.W., Louwerse, A.L., van de Poll, N.E., 1988. Sexual behavior and sexual orientation of the female rat after hormonal treatment during various stages of development. Horm. Behav. 22, 100–115.
de la Torre, B., Sjöberg, B., Hedman, M., Bártfai, G., Diczfalusy, E., 1981. A study of the short-time variation and interrelationship of plasma hormone levels reflecting pituitary, adrenocortical and testicular function in fertile men. Int. J. Androl. 4, 532–545.
de Rooij, S.R., Wouters, H., Yonker, J.E., Painter, R.C., Roseboom, T.J., 2010. Prenatal undernutrition and cognitive function in late adulthood. Proc. Natl. Acad. Sci. U. S. A. 107, 16881–16886.
de Souza Silva, M.A., Mattern, C., Topic, B., Buddenberg, T.E., Huston, J.P., 2009. Dopaminergic and serotonergic activity in neostriatum and nucleus accumbens enhanced by intranasal administration of testosterone. Eur. Neuropsychopharmacol. 19, 53–63.
De Vries, T.J., Schoffelmeer, A.N.M., Binnekade, R., Raasø, H., Vanderschuren, L.J.M.J., 2002. Relapse to cocaine- and heroin-seeking behavior mediated by dopamine D2 receptors is time-dependent and associated with behavioral sensitization. Neuropsychopharmacology 26, 18–26.
De Waele, J.P., Gianoulakis, C., 1993. Effects of single and repeated exposures to ethanol on hypothalamic beta-endorphin and CRH release by the C57BL/6 and DBA/2 strains of mice. Neuroendocrinology 57, 700–709.
De Waele, J.P., Papachristou, D.N., Gianoulakis, C., 1992. The alcohol-preferring C57BL/6 mice present an enhanced sensitivity of the hypothalamic beta-endorphin system to ethanol than the alcohol-avoiding DBA/2 mice. J. Pharmacol. Exp. Ther. 261, 788–794.
Den Hond, E., Dhooge, W., Bruckers, L., Schoeters, G., Nelen, V., van de Mieroop, E., Koppen, G., Bilau, M., Schroijen, C., Keune, H., Baeyens, W., van Larebeke, N., 2011. Internal exposure to pollutants and sexual maturation in Flemish adolescents. J. Expo. Sci. Environ. Epidemiol. 21, 224–233.
Denny, K., 2009. Handedness and depression: evidence from a large population survey. Laterality 14, 246–255.
Denny, K., 2011. Handedness and drinking behaviour. Br. J. Health Psychol. 16, 386–395.
Deshmukh, A., Rosenbloom, M.J., Sassoon, S., O'Reilly, A., Pfefferbaum, A., Sullivan, E.V., 2003. Alcoholic men endorse more DSM-IV withdrawal symptoms than alcoholic women matched in drinking history. J. Stud. Alcohol 64, 375–379.
Dettling, A., Fischer, F., Böhler, S., Ulrichs, F., Skopp, G., Graw, M., Haffner, H.T., 2007. Ethanol elimination rates in men and women in consideration of the calculated liver weight. Alcohol 41, 415–420.
Devaud, L.L., Chadda, R., 2001. Sex differences in rats in the development of and recovery from ethanol dependence assessed by changes in seizure susceptibility. Alcohol. Clin. Exp. Res. 25, 1689–1696.
Devaud, L.L., Risinger, F.O., Selvage, D., 2006. Impact of the hormonal milieu on the neurobiology of alcohol dependence and withdrawal. J. Gen. Psychol. 133, 337–356.
Devor, E.J., Cloninger, C.R., 1989. Genetics of alcoholism. Annu. Rev. Genet. 23, 19–36.
Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M.A., Spina, L., Cadoni, C., Acquas, E., Carboni, E., Valentini, V., Lecca, D., 2004. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology 47 (Suppl. 1), 227–241.
Di Chiara, G., Imperato, A., 1988a. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5278.

Di Chiara, G., Imperato, A., 1988b. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244, 1067–1080.
Di Paolo, T., Rouillard, C., Bédard, P., 1985. 17 beta-Estradiol at a physiological dose acutely increases dopamine turnover in rat brain. Eur. J. Pharmacol. 117, 197–203.
Diana, M., Rossetti, Z.L., Gessa, G., 1993. Rewarding and aversive effects of ethanol: interplay of GABA, glutamate and dopamine. Alcohol Alcohol. Suppl. 2, 315–319.
Dick, D.M., Rose, R.J., Viken, R.J., Kaprio, J., 2000. Pubertal timing and substance use: associations between and within families across late adolescence. Dev. Psychol. 36, 180–189.
Domellöf, E., Rönnqvist, L., Titran, M., Esseily, R., Fagard, J., 2009. Atypical functional lateralization in children with fetal alcohol syndrome. Dev. Psychobiol. 51, 696–705.
Doremus, T.L., Brunell, S.C., Rajendran, P., Spear, L.P., 2005. Factors influencing elevated ethanol consumption in adolescent relative to adult rats. Alcohol. Clin. Exp. Res. 29, 1796–1808.
Doty, R.L., Kisat, M., Tourbier, I., 2008. Estrogen replacement therapy induces functional asymmetry on an odor memory/discrimination test. Brain Res. 1214, 35–39.
Doyen, A.L., Dufour, T., Caroff, X., Cherfouh, A., Carlier, M., 2008. Hand preference and hand performance: cross-sectional developmental trends and family resemblance in degree of laterality. Laterality 13, 179–197.
Dreher, J.C., Schmidt, P.J., Kohn, P., Furman, D., Rubinow, D., Berman, K.F., 2007. Menstrual cycle phase modulates reward-related neural function in women. Proc. Natl. Acad. Sci. U. S. A. 104, 2465–2470.
DuRant, R.H., Rickert, V.I., Ashworth, C.S., Newman, C., Slavens, G., 1993. Use of multiple drugs among adolescents who use anabolic steroids. N. Engl. J. Med. 328, 922–926.
Dyment, P.G., 1987. The adolescent athlete and ergogenic aids. J. Adolesc. Health Care 8, 68–73.
Edenberg, H.J., 2007. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res. Health 30, 5–13.
Ehrenkranz, J., Bliss, E., Sheard, M.H., 1974. Plasma testosterone: correlation with aggressive behavior and social dominance in man. Psychosom. Med. 36, 469–475.
Eichmann, F., Holst, D.V., 1999. Organization of territorial marking behavior by testosterone during puberty in male tree shrews. Physiol. Behav. 65, 785–791.
Emanuele, M.A., LaPaglia, N., Steiner, J., Jabamoni, K., Hansen, M., Kirsteins, L., Emanuele, N.V., 1998. Reversal of ethanol-induced testosterone suppression in peripubertal male rats by opiate blockade. Alcohol. Clin. Exp. Res. 22, 1199–1204.
Emaus, A., Veierød, M.B., Furberg, A.S., Espetvedt, S., Friedenreich, C., Ellison, P.T., Jasienska, G., Andersen, L.B., Thune, I., 2008. Physical activity, heart rate, metabolic profile, and estradiol in premenopausal women. Med. Sci. Sports Exerc. 40, 1022–1030.
Ericson, M., Molander, A., Löf, E., Engel, J.A., Söderpalm, B., 2003. Ethanol elevates accumbal dopamine levels via indirect activation of ventral tegmental nicotinic acetylcholine receptors. Eur. J. Pharmacol. 467, 85–93.
Eriksson, C.J.P., Fukunaga, T., Lindman, R., 1994. Sex hormone response to alcohol. Nature 369, 711.
Eriksson, C.J.P., Fukunaga, T., Sarkola, T., Lindholm, H., Ahola, L., 1996. Estrogen-related acetaldehyde elevation in women during alcohol intoxication. Alcohol. Clin. Exp. Res. 20, 1192–1195.
Eriksson, C.J.P., Kaprio, J., Pulkkinen, L., Rose, R.J., 2005. Testosterone and alcohol use among adolescent male twins: testing between-family associations in within-family comparisons. Behav. Genet. 35, 359–368.
Eriksson, C.J.P., von der Pahlen, B., Sarkola, T., Seppä, K., 2003. Oestradiol and human male alcohol-related aggression. Alcohol Alcohol. 38, 589–596.
Eriksson, C.J.P., Widenius, T.V., Ylikahri, R.H., Härkönen, M., Leinonen, P., 1983. Inhibition of testosterone biosynthesis by ethanol. Relation to hepatic and testicular acetaldehyde, ketone bodies and cytosolic redox state in rats. Biochem. J. 210, 29–36.
Everitt, B.J., Dickinson, A., Robbins, T.W., 2001. The neuropsychological basis of addictive behaviour. Brain Res. Brain Res. Rev. 36, 129–138.
Fahlke, C., Engel, J.A., Eriksson, C.J.P., Hård, E., Söderpalm, B., 1994a. Involvement of corticosterone in the modulation of ethanol consumption in the rat. Alcohol 11, 195–202.
Fahlke, C., Hård, E., Eriksson, C.J.P., Engel, J.A., Hansen, S., 1995. Consequence of long-term exposure to corticosterone or dexamethasone on ethanol consumption in the adrenalectomized rat, and the effect of type I and type II corticosteroid receptor antagonists. Psychopharmacology (Berl.) 117, 216–224.
Fahlke, C., Hård, E., Thomasson, R., Engel, J.A., Hansen, S., 1994b. Metyrapone-induced suppression of corticosterone synthesis reduces ethanol consumption in high-preferring rats. Pharmacol. Biochem. Behav. 48, 977–981.
Faingold, C.L., N'Gouemo, P., Riaz, A., 1998. Ethanol and neurotransmitter interactions—from molecular to integrative effects. Prog. Neurobiol. 55, 509–535.
Farabegoli, F., Barbi, C., Lambertini, E., Piva, R., 2007. (−)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells. Cancer Detect. Prev. 31, 499–504.
Fergusson, D.M., Horwood, L.J., Lynskey, M.T., 1995. The prevalence and risk factors associated with abusive or hazardous alcohol consumption in 16-year-olds. Addiction 90, 935–946.
Fillmore, K.M., Golding, J.M., Kniep, S., Leino, E.V., Shoemaker, C., Ager, C.R., Ferrer, H.P., Ahlstrom, S., Allebeck, P., Amundsen, A., et al., 1995. Gender differences for the risk of alcohol-related problems in multiple national contexts. Recent Dev. Alcohol. 12, 409–439.
Fink, B., Manning, J.T., Neave, N., Tan, U., 2004. Second to fourth digit ratio and hand skill in Austrian children. Biol. Psychol. 67, 375–384.
Foradori, C.D., Weiser, M.J., Handa, R.J., 2008. Non-genomic actions of androgens. Front. Neuroendocrinol. 29, 169–181.
Ford, M.M., Nickel, J.D., Finn, D.A., 2005. Treatment with and withdrawal from finasteride alter ethanol intake patterns in male C57BL/6J mice: potential role of endogenous neurosteroids? Alcohol 37, 23–33.
Ford, M.M., Yoneyama, N., Strong, M.N., Fretwell, A., Tanchuck, M., Finn, D.A., 2008. Inhibition of 5alpha-reduced steroid biosynthesis impedes acquisition of ethanol drinking in male C57BL/6J mice. Alcohol. Clin. Exp. Res. 32, 1408–1416.
Forger, N.G., Morin, L.P., 1982. Reproductive state modulates ethanol intake in rats: effects of ovariectomy, ethanol concentration, estrous cycle and pregnancy. Pharmacol. Biochem. Behav. 17, 323–331.
Forquer, M.R., Hashimoto, J.G., Roberts, M.L., Wiren, K.M., 2011. Elevated testosterone in females reveals a robust sex difference in altered androgen levels during chronic alcohol withdrawal. Alcohol 45, 161–171.
Forstmeier, W., Mueller, J.C., Kempenaers, B., 2010. A polymorphism in the oestrogen receptor gene explains covariance between digit ratio and mating behaviour. Proc. Biol. Sci. 277, 3353–3361.
Franzek, E.J., Sprangers, N., Janssens, A.C.J.W., Van Duijn, C.M., Van De Wetering, B.J.M., 2008. Prenatal exposure to the 1944–45 Dutch 'hunger winter' and addiction later in life. Addiction 103, 433–438.
Frias, J., Rodriguez, R., Torres, J.M., Ruiz, E., Ortega, E., 2000. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adolescents of both sexes. Life Sci. 67, 1081–1086.
Frias, J., Torres, J.M., Miranda, M.T., Ruiz, E., Ortega, E., 2002. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adults of both sexes. Alcohol Alcohol. 37, 169–173.
Friedenreich, C.M., Neilson, H.K., Lynch, B.M., 2010. State of the epidemiological evidence on physical activity and cancer prevention. Eur. J. Cancer 46, 2593–2604.
Froehlich, J.C., Harts, J., Lumeng, L., Li, T.K., 1990. Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. Pharmacol. Biochem. Behav. 35, 385–390.
Fuxjager, M.J., Forbes-Lorman, R.M., Coss, D.J., Auger, C.J., Auger, A.P., Marler, C.A., 2010. Winning territorial disputes selectively enhances androgen sensitivity in neural pathways related to motivation and social aggression. Proc. Natl. Acad. Sci. U. S. A. 107, 12393–12398.
Gade-Andavolu, R., MacMurray, J., Comings, D.E., Calati, R., Chiesa, A., Serretti, A., 2009. Association between the estrogen receptor TA polymorphism and harm avoidance. Neurosci. Lett. 467, 155–158.
Gadea, M., Gómez, C., González-Bono, E., Salvador, A., Espert, R., 2003. Salivary testosterone is related to both handedness and degree of linguistic lateralization in normal women. Psychoneuroendocrinology 28, 274–287.
Gallucci, W.T., Baum, A., Laue, L., Rabin, D.S., Chrousos, G.P., Gold, P.W., Kling, M.A., 1993. Sex differences in sensitivity of the hypothalamic-pituitary-adrenal axis. Health Psychol. 12, 420–425.
Gear, R.W., Gordon, N.C., Heller, P.H., Paul, S., Miaskowski, C., Levine, J.D., 1996a. Gender difference in analgesic response to the kappa-opioid pentazocine. Neurosci. Lett. 205, 207–209.
Gear, R.W., Gordon, N.C., Miaskowski, C., Paul, S.M., Heller, P.H., Levine, J.D., 2003. Sexual dimorphism in very low dose nalbuphine postoperative analgesia. Neurosci. Lett. 339, 1–4.
Gear, R.W., Miaskowski, C., Gordon, N.C., Paul, S.M., Heller, P.H., Levine, J.D., 1996b. Kappa-opioids produce significantly greater analgesia in women than in men. Nat. Med. 2, 1248–1250.
Gene Ontology Consortium, 2006. The Gene Ontology (GO) project in 2006. Nucleic Acids Res. 34, D322–326.
Gerra, G., Leonardi, C., Cortese, E., Zaimovic, A., Dell'Agnello, G., Manfredini, M., Somaini, L., Petracca, F., Caretti, V., Baroni, C., Donnini, C., 2008. Adrenocorticotropic hormone and cortisol plasma levels directly correlate with childhood neglect and depression measures in addicted patients. Addict. Biol. 13, 95–104.
Geschwind, N., Behan, P., 1982. Left-handedness: association with immune disease, migraine, and developmental learning disorder. Proc. Natl. Acad. Sci. U. S. A. 79, 5097–5100.
Geschwind, N., Galaburda, A.M., 1985. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch. Neurol. 42, 428–459.
Giannini, A.J., Martin, D.M., Turner, C.E., 1990. Beta-endorphin decline in late luteal phase dysphoric disorder. Int. J. Psychiatry Med. 20, 279–284.
Gianoulakis, C., 1996. Implications of endogenous opioids and dopamine in alcoholism: human and basic science studies. Alcohol Alcohol. Suppl. 1, 33–42.
Gianoulakis, C., 2001. Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism. J. Psychiatry Neurosci. 26, 304–318.
Gianoulakis, C., Dai, X., Brown, T., 2003. Effect of chronic alcohol consumption on the activity of the hypothalamic-pituitary-adrenal axis and pituitary beta-endorphin as a function of alcohol intake, age, and gender. Alcohol. Clin. Exp. Res. 27, 410–423.
Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.

Giedd, J.N., Clasen, L.S., Lenroot, R., Greenstein, D., Wallace, G.L., Ordaz, S., Molloy, E.A., Blumenthal, J.D., Tossell, J.W., Stayer, C., Samango-Sprouse, C.A., Shen, D., Davatzikos, C., Merke, D., Chrousos, G.P., 2006. Puberty-related influences on brain development. Mol. Cell. Endocrinol. 254–255, 154–162.

Giedd, J.N., Lalonde, F.M., Celano, M.J., White, S.L., Wallace, G.L., Lee, N.R., Lenroot, R.K., 2009. Anatomical brain magnetic resonance imaging of typically developing children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 48, 465–470.

Giegling, I., Chiesa, A., Calati, R., Hartmann, A.M., Möller, H.J., De Ronchi, D., Rujescu, D., Serretti, A., 2009. Do the estrogen receptors 1 gene variants influence the temperament and character inventory scores in suicidal attempters and healthy subjects? Am. J. Med. Genet. B Neuropsychiatr. Genet. 150B, 434–438.

Gilbert, A.N., Wysocki, C.J., 1992. Hand preference and age in the United States. Neuropsychologia 30, 601–608.

Goeders, N.E., 2002. The HPA axis and cocaine reinforcement. Psychoneuroendocrinology 27, 13–33.

Goh, V.H.H., Tong, T.Y.Y., 2011. The moderating impact of lifestyle factors on sex steroids, sexual activities and aging in Asian men. Asian J. Androl..

Goh, V.H.H., Tong, T.Y.Y., Mok, H.P.P., Said, B., 2007. Interactions among age, adiposity, bodyweight, lifestyle factors and sex steroid hormones in healthy Singaporean Chinese men. Asian J. Androl. 9, 611–621.

Goodin, M.G., Rosengren, R.J., 2003. Epigallocatechin gallate modulates CYP450 isoforms in the female Swiss-Webster mouse. Toxicol. Sci. 76, 262–270.

Gordon, J.H., Fields, J.Z., 1989. A permanent dopamine receptor up-regulation in the ovariectomized rat. Pharmacol. Biochem. Behav. 33, 123–125.

Grahame, N.J., Low, M.J., Cunningham, C.L., 1998. Intravenous self-administration of ethanol in beta-endorphin-deficient mice. Alcohol. Clin. Exp. Res. 22, 1093–1098.

Grant, K.A., Johanson, C.E., 1988. Oral ethanol self-administration in free-feeding rhesus monkeys. Alcohol. Clin. Exp. Res. 12, 780–784.

Greenfield, T.K., Rogers, J.D., 1999. Who drinks most of the alcohol in the US? The policy implications. J. Stud. Alcohol 60, 78–89.

Guillemin, R., Vargo, T., Rossier, J., Minick, S., Ling, N., Rivier, C., Vale, W., Bloom, F., 1977. beta-Endorphin and adrenocorticotropin are selected concomitantly by the pituitary gland. Science 197, 1367–1369.

Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. 20, 2369–2382.

Hall, S.A., Esche, G.R., Araujo, A.B., Travison, T.G., Clark, R.V., Williams, R.E., McKinlay, J.B., 2008. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J. Clin. Endocrinol. Metab. 93, 3870–3877.

Hammer Jr., R.P., Bogic, L., Handa, R.J., 1993. Estrogenic regulation of proenkephalin mRNA expression in the ventromedial hypothalamus of the adult male rat. Brain Res. Mol. Brain Res. 19, 129–134.

Hammer Jr., R.P., Bridges, R.S., 1987. Preoptic area opioids and opiate receptors increase during pregnancy and decrease during lactation. Brain Res. 420, 48–56.

Hammond, J., Le, Q., Goodyer, C., Gelfand, M., Trifiro, M., LeBlanc, A., 2001. Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. J. Neurochem. 77, 1319–1326.

Harburg, E., 1981. Handedness and drinking–smoking types. Percept. Mot. Skills 52, 279–282.

Harford, T.C., Parker, D.A., Grant, B.F., Dawson, D.A., 1992. Alcohol use and dependence among employed men and women in the United States in 1988. Alcohol. Clin. Exp. Res. 16, 146–148.

Harrell, J.S., Bangdiwala, S.I., Deng, S., Webb, J.P., Bradley, C., 1998. Smoking initiation in youth: the roles of gender, race, socioeconomics, and developmental status. J. Adolesc. Health 23, 271–279.

Harvey, S.M., Beckman, L.J., 1985. Cyclic fluctuation in alcohol consumption among female social drinkers. Alcohol. Clin. Exp. Res. 9, 465–471.

Hasselblatt, M., Krieg-Hartig, C., Hüfner, M., Halaris, A., Ehrenreich, H., 2003. Persistent disturbance of the hypothalamic-pituitary-gonadal axis in abstinent alcoholic men. Alcohol Alcohol. 38, 239–242.

Hauck, J.A., Dewey, D., 2001. Hand preference and motor functioning in children with autism. J. Autism Dev. Disord. 31, 265–277.

Hausmann, M., 2005. Hemispheric asymmetry in spatial attention across the menstrual cycle. Neuropsychologia 43, 1559–1567.

Hausmann, M., Güntürkün, O., 2000. Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. Neuropsychologia 38, 1362–1374.

Hecht, D., 2010. Depression and the hyperactive right-hemisphere. Neurosci. Res. 68, 77–87.

Heemers, H.V., Tindall, D.J., 2007. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. Endocr. Rev. 28, 778–808.

Heilig, M., Koob, G.F., 2007. A key role for corticotropin-releasing factor in alcohol dependence. Trends Neurosci. 30, 399–406.

Heinz, A., Rommelspacher, H., Gräf, K.J., Kürten, I., Otto, M., Baumgartner, A., 1995. Hypothalamic-pituitary-gonadal axis, prolactin, and cortisol in alcoholics during withdrawal and after three weeks of abstinence: comparison with healthy control subjects. Psychiatry Res. 56, 81–95.

Hernandez, L., Gonzalez, L., Murzi, E., Páez, X., Gottberg, E., Baptista, T., 1994. Testosterone modulates mesolimbic dopaminergic activity in male rats. Neurosci. Lett. 171, 172–174.

Herz, A., 1997. Endogenous opioid systems and alcohol addiction. Psychopharmacology (Berl.) 129, 99–111.

Heuser, I.J., Gotthardt, U., Schweiger, U., Schmider, J., Lammers, C.H., Dettling, M., Holsboer, F., 1994. Age-associated changes of pituitary–adrenocortical hormone regulation in humans: importance of gender. Neurobiol. Aging 15, 227–231.

Hibell, B., Guttormsson, U., Ahlström, S., Balakireva, O., Bjarnason, T., Kokkevi, A., Kraus, L., 2009. The 2007 ESPAD Report: Substance Use Among Students in 35 European Countries. http://www.espad.org/espad-reports, accessed: 28 May 2011.

Hier, D.B., Crowley Jr., W.F., 1982. Spatial ability in androgen-deficient men. N. Engl. J. Med. 306, 1202–1205.

Hilakivi-Clarke, L., 1996. Role of estradiol in alcohol intake and alcohol-related behaviors. J. Stud. Alcohol 57, 162–170.

Hill, E.M., Chow, K., 2002. Life-history theory and risky drinking. Addiction 97, 401–413.

Hillemacher, T., Bleich, S., Frieling, H., Schanze, A., Wilhelm, J., Sperling, W., Kornhuber, J., Kraus, T., 2007. Evidence of an association of leptin serum levels and craving in alcohol dependence. Psychoneuroendocrinology 32, 87–90.

Hillemacher, T., Weinland, C., Heberlein, A., Gröschl, M., Schanze, A., Frieling, H., Wilhelm, J., Kornhuber, J., Bleich, S., 2009. Increased levels of adiponectin and resistin in alcohol dependence—possible link to craving. Drug Alcohol Depend. 99, 333–337.

Hiney, J.K., Dees, W.L., 1991. Ethanol inhibits luteinizing hormone-releasing hormone release from the median eminence of prepubertal female rats in vitro: investigation of its actions on norepinephrine and prostaglandin-E2. Endocrinology 128, 1404–1408.

Hoek, H.W., Brown, A.S., Susser, E., 1998. The Dutch famine and schizophrenia spectrum disorders. Soc. Psychiatry Psychiatr. Epidemiol. 33, 373–379.

Hoekstra, R.A., Bartels, M., Boomsma, D.I., 2006. Heritability of testosterone levels in 12-year-old twins and its relation to pubertal development. Twin Res. Hum. Genet. 9, 558–565.

Hoffman, P.N., Cleveland, D.W., Griffin, J.W., Landes, P.W., Cowan, N.J., Price, D.L., 1987. Neurofilament gene expression: a major determinant of axonal caliber. Proc. Natl. Acad. Sci. U. S. A. 84, 3472–3476.

Holdstock, L., de Wit, H., 2000. Effects of ethanol at four phases of the menstrual cycle. Psychopharmacology (Berl.) 150, 374–382.

Hommel, J.D., Trinko, R., Sears, R.M., Georgescu, D., Liu, Z.W., Gao, X.B., Thurmon, J.J., Marinelli, M., DiLeone, R.J., 2006. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron 51, 801–810.

Hommer, D.W., 2003. Male and female sensitivity to alcohol-induced brain damage. Alcohol Res. Health 27, 181–185.

Hönekopp, J., Bartholdt, L., Beier, L., Liebert, A., 2007. Second to fourth digit length ratio (2D:4D) and adult sex hormone levels: new data and a meta-analytic review. Psychoneuroendocrinology 32, 313–321.

Hönekopp, J., Manning, J.T., Müller, C., 2006. Digit ratio (2D:4D) and physical fitness in males and females: evidence for effects of prenatal androgens on sexually selected traits. Horm. Behav. 49, 545–549.

Hönekopp, J., Watson, S., 2010. Meta-analysis of digit ratio 2D:4D shows greater sex difference in the right hand. Am. J. Hum. Biol. 22, 619–630.

Hurd, P.L., Vaillancourt, K.L., Dinsdale, N.L., 2010. Aggression, digit ratio and variation in androgen receptor and monoamine oxidase A genes in men. Behav. Genet. 41, 543–556.

Irvine, R.A., Ma, H., Yu, M.C., Ross, R.K., Stallcup, M.R., Coetzee, G.A., 2000. Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. Hum. Mol. Genet. 9, 267–274.

Jackson, C., 2008. Prediction of hemispheric asymmetry as measured by handedness from digit length and 2D:4D digit ratio. Laterality 13, 34–50.

Järveläinen, H.A., Lukkari, T.A., Heinaro, S., Sippel, H., Lindros, K.O., 2001. The antiestrogen toremifene protects against alcoholic liver injury in female rats. J. Hepatol. 35, 46–52.

Jasienska, G., Kapiszewska, M., Ellison, P.T., Kalemba-Drozdz, M., Nenko, I., Thune, I., Ziomkiewicz, A., 2006. CYP17 genotypes differ in salivary 17-beta estradiol levels: a study based on hormonal profiles from entire menstrual cycles. Cancer Epidemiol. Biomarkers Prev. 15, 2131–2135.

Jellinek, E.M., 1960. The Disease Concept of Alcoholism. Hillhouse Press, New Brunswick.

Jenab, S., Morris, P.L., 2000. Interleukin-6 regulation of kappa opioid receptor gene expression in primary Sertoli cells. Endocrine 13, 11–15.

Johansson, P., Lindqvist, A., Nyberg, F., Fahlke, C., 2000. Anabolic androgenic steroids affects alcohol intake, defensive behaviors and brain opioid peptides in the rat. Pharmacol. Biochem. Behav. 67, 271–279.

Johansson, P., Ray, A., Zhou, Q., Huang, W., Karlsson, K., Nyberg, F., 1997. Anabolic androgenic steroids increase beta-endorphin levels in the ventral tegmental area in the male rat brain. Neurosci. Res. 27, 185–189.

Johnston, A.L., File, S.E., 1991. Sex differences in animal tests of anxiety. Physiol. Behav. 49, 245–250.

Juárez, J., Barrios de Tomasi, E., 1999. Sex differences in alcohol drinking patterns during forced and voluntary consumption in rats. Alcohol 19, 15–22.

Juárez, J., Barrios De Tomasi, E., Virgen, M., 2002. Effects of estradiol treatment on voluntary and forced alcohol consumption in male rats. Pharmacol. Biochem. Behav. 71, 259–268.

Jurimäe, T., Voracek, M., Jurimäe, J., Lätt, E., Haljaste, K., Saar, M., Purge, P., 2008. Relationships between finger-length ratios, ghrelin, leptin, IGF axis, and sex steroids in young male and female swimmers. Eur. J. Appl. Physiol. 104, 523–529.

Kanayama, G., Brower, K.J., Wood, R.I., Hudson, J.I., Pope Jr., H.G., 2009. Anabolic-androgenic steroid dependence: an emerging disorder. Addiction 104, 1966–1978.
Kanayama, G., Hudson, J.I., Pope Jr., H.G., 2010. Illicit anabolic-androgenic steroid use. Horm. Behav. 58, 111–121.
Kashkin, K.B., Kleber, H.D., 1989. Hooked on hormones? An anabolic steroid addiction hypothesis. JAMA 262, 3166–3170.
Katz, N., Mazer, N.A., 2009. The impact of opioids on the endocrine system. Clin. J. Pain 25, 170–175.
Kelley, A.E., 2004. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron 44, 161–179.
Kelley, A.E., Bakshi, V.P., Haber, S.N., Steininger, T.L., Will, M.J., Zhang, M., 2002. Opioid modulation of taste hedonics within the ventral striatum. Physiol. Behav. 76, 365–377.
Kelly, M.J., Qiu, J., Rønnekleiv, O.K., 2003. Estrogen modulation of G-protein-coupled receptor activation of potassium channels in the central nervous system. Ann. N. Y. Acad. Sci. 1007, 6–16.
Kerkhof, G.F., Leunissen, R.W.J., Willemsen, R.H., de Jong, F.H., Stijnen, T., Hokken-Koelega, A.C.S., 2009. Influence of preterm birth and birth size on gonadal function in young men. J. Clin. Endocrinol. Metab. 94, 4243–4250.
Kerr, J.E., Allore, R.J., Beck, S.G., Handa, R.J., 1995. Distribution and hormonal regulation of androgen receptor (AR) and AR messenger ribonucleic acid in the rat hippocampus. Endocrinology 136, 3213–3221.
Kidokoro, K., Ino, K., Hirose, K., Kajiyama, H., Hosono, S., Suzuki, T., Kawase, T., Hiraki, A., Hamajima, N., Tanaka, H., Tajima, K., Kikkawa, F., Matsuo, K., 2009. Association between CYP19A1 polymorphisms and sex hormones in postmenopausal Japanese women. J. Hum. Genet. 54, 78–85.
Kiefer, F., Jahn, H., Jaschinski, M., Holzbach, R., Wolf, K., Naber, D., Wiedemann, K., 2001a. Leptin: a modulator of alcohol craving? Biol. Psychiatry 49, 782–787.
Kiefer, F., Jahn, H., Kellner, M., Naber, D., Wiedemann, K., 2001b. Leptin as a possible modulator of craving for alcohol. Arch. Gen. Psychiatry 58, 509–510.
Kiefer, F., Jahn, H., Otte, C., Demiralay, C., Wolf, K., Wiedemann, K., 2005. Increasing leptin precedes craving and relapse during pharmacological abstinence maintenance treatment of alcoholism. J. Psychiatr. Res. 39, 545–551.
Kimura, M., Higuchi, S., 2011. Genetics of alcohol dependence. Psychiatry Clin. Neurosci. 65, 213–225.
King, A.C., Bernardy, N.C., Hauner, K., 2003. Stressful events, personality, and mood disturbance: gender differences in alcoholics and problem drinkers. Addict. Behav. 28, 171–187.
King, A.C., Errico, A.L., Parsons, O.A., 1995. Eysenck's personality dimensions and sex steroids in male abstinent alcoholics and nonalcoholics: an exploratory study. Biol. Psychol. 39, 103–113.
Kirschbaum, C., Klauer, T., Filipp, S.H., Hellhammer, D.H., 1995a. Sex-specific effects of social support on cortisol and subjective responses to acute psychological stress. Psychosom. Med. 57, 23–31.
Kirschbaum, C., Kudielka, B.M., Gaab, J., Schommer, N.C., Hellhammer, D.H., 1999. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom. Med. 61, 154–162.
Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1995b. Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. Psychoneuroendocrinology 20, 509–514.
Kishimoto, R., Ogishi, Y., Ueda, M., Matsusaki, M., Amako, K., Goda, K., Park, S.S., 2002. Gender-related differences in mouse hepatic ethanol metabolism. J. Nutr. Sci. Vitaminol. (Tokyo) 48, 216–224.
Klar, A.J.S., 1999. Genetic models for handedness, brain lateralization, schizophrenia, and manic-depression. Schizophr. Res. 39, 207–218.
Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., Ringelstein, E.B., Henningsen, H., 2000. Handedness and hemispheric language dominance in healthy humans. Brain 123 (Pt. 12), 2512–2518.
Knopik, V.S., Heath, A.C., Madden, P.A.F., Bucholz, K.K., Slutske, W.S., Nelson, E.C., Statham, D., Whitfield, J.B., Martin, N.G., 2004. Genetic effects on alcohol dependence risk: re-evaluating the importance of psychiatric and other heritable risk factors. Psychol. Med. 34, 1519–1530.
Koob, G.F., Roberts, A.J., Schulteis, G., Parsons, L.H., Heyser, C.J., Hyytiä, P., Merlo-Pich, E., Weiss, F., 1998. Neurocircuitry targets in ethanol reward and dependence. Alcohol. Clin. Exp. Res. 22, 3–9.
Kornhuber, J., Erhard, G., Lenz, B., Kraus, T., Sperling, W., Bayerlein, K., Biermann, T., Stoessel, C., 2011. Low digit ratio 2D:4D in alcohol dependent patients. PLoS ONE 6, e19332.
Kotani, Y., Yokota, I., Kitamura, S., Matsuda, J., Naito, E., Kuroda, Y., 2004. Plasma adiponectin levels in newborns are higher than those in adults and positively correlated with birth weight. Clin. Endocrinol. (Oxf.) 61, 418–423.
Kouri, E.M., Lukas, S.E., Pope Jr., H.G., Oliva, P.S., 1995. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. Drug Alcohol Depend. 40, 73–79.
Kranzler, H.R., Edenberg, H.J., 2010. Pharmacogenetics of alcohol and alcohol dependence treatment. Curr. Pharm. Des. 16, 2141–2148.
Kren, M.C., Haller, V.L., Welch, S.P., 2008. The role of gonadal hormones on opioid receptor protein density in arthritic rats. Eur. J. Pharmacol. 578, 177–184.
Krishnan-Sarin, S., Jing, S.L., Kurtz, D.L., Zweifel, M., Portoghese, P.S., Li, T.K., Froehlich, J.C., 1995a. The delta opioid receptor antagonist naltrindole attenuates both alcohol and saccharin intake in rats selectively bred for alcohol preference. Psychopharmacology (Berl.) 120, 177–185.
Krishnan-Sarin, S., Portoghese, P.S., Li, T.K., Froehlich, J.C., 1995b. The delta 2-opioid receptor antagonist naltriben selectively attenuates alcohol intake in rats bred for alcohol preference. Pharmacol. Biochem. Behav. 52, 153–159.
Krishnan-Sarin, S., Wand, G.S., Li, X.W., Portoghese, P.S., Froehlich, J.C., 1998. Effect of mu opioid receptor blockade on alcohol intake in rats bred for high alcohol drinking. Pharmacol. Biochem. Behav. 59, 627–635.
Krithivas, K., Yurgalevitch, S.M., Mohr, B.A., Wilcox, C.J., Batter, S.J., Brown, M., Longcope, C., McKinlay, J.B., Kantoff, P.W., 1999. Evidence that the CAG repeat in the androgen receptor gene is associated with the age-related decline in serum androgen levels in men. J. Endocrinol. 162, 137–142.
Kritzer, M.F., 1997. Selective colocalization of immunoreactivity for intracellular gonadal hormone receptors and tyrosine hydroxylase in the ventral tegmental area, substantia nigra, and retrorubral fields in the rat. J. Comp. Neurol. 379, 247–260.
Kudielka, B.M., Hellhammer, J., Hellhammer, D.H., Wolf, O.T., Pirke, K.M., Varadi, E., Pilz, J., Kirschbaum, C., 1998. Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. J. Clin. Endocrinol. Metab. 83, 1756–1761.
Kumar, R.C., Thakur, M.K., 2004. Androgen receptor mRNA is inversely regulated by testosterone and estradiol in adult mouse brain. Neurobiol. Aging 25, 925–933.
Kuntsche, E., Knibbe, R., Gmel, G., Engels, R., 2005. Why do young people drink? A review of drinking motives. Clin. Psychol. Rev. 25, 841–861.
Künzel, H.E., Binder, E.B., Nickel, T., Ising, M., Fuchs, B., Majer, M., Pfennig, A., Ernst, G., Kern, N., Schmid, D.A., Uhr, M., Holsboer, F., Modell, S., 2003. Pharmacological and nonpharmacological factors influencing hypothalamic-pituitary-adrenocortical axis reactivity in acutely depressed psychiatric in-patients, measured by the Dex-CRH test. Neuropsychopharmacology 28, 2169–2178.
Kurling-Kailanto, S., Kankaanpää, A., Hautaniemi, J., Seppälä, T., 2010. Blockade of androgen or estrogen receptors reduces nandrolone's ability to modulate acute reward-related neurochemical effects of amphetamine in rat brain. Pharmacol. Biochem. Behav. 95, 422–427.
La Grange, L., Jones, T.D., Erb, L., Reyes, E., 1995. Alcohol consumption: biochemical and personality correlates in a college student population. Addict. Behav. 20, 93–103.
Lakoza, G.N., Barkov, N.K., 1980. The role of testosterone in the development of experimental alcoholism. Bull. Narc. 32, 41–48.
Lamblin, F., De Witte, P., 1996. Adrenalectomy prevents the development of alcohol preference in male rats. Alcohol 13, 233–238.
Lammers, C.H., D'Souza, U., Qin, Z.H., Lee, S.H., Yajima, S., Mouradian, M.M., 1999. Regulation of striatal dopamine receptors by estrogen. Synapse 34, 222–227.
Lancaster, F.E., Brown, T.D., Coker, K.L., Elliott, J.A., Wren, S.B., 1996. Sex differences in alcohol preference and drinking patterns emerge during the early postpubertal period. Alcohol. Clin. Exp. Res. 20, 1043–1049.
Lancaster, F.E., Spiegel, K.S., 1992. Sex differences in pattern of drinking. Alcohol 9, 415–420.
Landry, M., Lévesque, D., Di Paolo, T., 2002. Estrogenic properties of raloxifene, but not tamoxifen, on D2 and D3 dopamine receptors in the rat forebrain. Neuroendocrinology 76, 214–222.
Lanza, S.T., Collins, L.M., 2002. Pubertal timing and the onset of substance use in females during early adolescence. Prev. Sci. 3, 69–82.
Lavikainen, H., Ahlström, S., Metso, L., Nevalainen, J., Lintonen, T., 2008. Relationship between negative experiences and drinking experience among 15- to 16-year-old adolescents in Finland. Eur. Addict. Res. 14, 169–178.
Le Moal, M., Simon, H., 1991. Mesocorticolimbic dopaminergic network: functional and regulatory roles. Physiol. Rev. 71, 155–234.
Leggio, L., 2010. Role of the ghrelin system in alcoholism: acting on the growth hormone secretagogue receptor to treat alcohol-related diseases. Drug News Perspect. 23, 157–166.
Leinninger, G.M., Jo, Y.H., Leshan, R.L., Louis, G.W., Yang, H., Barrera, J.G., Wilson, H., Opland, D.M., Faouzi, M.A., Gong, Y., Jones, J.C., Rhodes, C.J., Chua Jr., S., Diano, S., Horvath, T.L., Seeley, R.J., Becker, J.B., Münzberg, H., Myers Jr., M.G., 2009. Leptin acts via leptin receptor-expressing lateral hypothalamic neurons to modulate the mesolimbic dopamine system and suppress feeding. Cell Metab. 10, 89–98.
Lejuez, C.W., Magidson, J.F., Mitchell, S.H., Sinha, R., Stevens, M.C., de Wit, H., 2010. Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. Alcohol. Clin. Exp. Res. 34, 1334–1345.
Lenroot, R.K., Giedd, J.N., 2006. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. Neurosci. Biobehav. Rev. 30, 718–729.
Lenroot, R.K., Gogtay, N., Greenstein, D.K., Wells, E.M., Wallace, G.L., Clasen, L.S., Blumenthal, J.D., Lerch, J., Zijdenbos, A.P., Evans, A.C., Thompson, P.M., Giedd, J.N., 2007. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36, 1065–1073.
Lenz, B., Frieling, H., Jacob, C., Heberlein, A., Kornhuber, J., Bleich, S., Hillemacher, T., 2010. The modulating effect of the androgen receptor on craving in alcohol withdrawal of men is partially mediated by leptin. Pharmacogenomics J. 10, 226–231.
Lenz, B., Heberlein, A., Bayerlein, K., Frieling, H., Kornhuber, J., Bleich, S., Hillemacher, T., 2011a. The TTTAn aromatase (CYP19A1) polymorphism is associated with compulsive craving of male patients during alcohol withdrawal. Psychoneuroendocrinology 36, 1261–1264.
Lenz, B., Heberlein, A., Weinland, C., Frieling, H., Kornhuber, J., Bleich, S., Hillemacher, T., 2011b. Androgen receptor polyglutamine length does not influence serum levels of adipocytokines in alcoholism: a preliminary retrospective analysis. Alcohol Alcohol. 46, 214–216.
Lenz, B., Jacob, C., Frieling, H., Jacobi, A., Hillemacher, T., Muschler, M., Watson, K., Kornhuber, J., Bleich, S., 2009. Polymorphism of the long polyglutamine tract in

the human androgen receptor influences craving of men in alcohol withdrawal. Psychoneuroendocrinology 34, 968–971.
Lenz, K.M., McCarthy, M.M., 2011. Organized for sex-steroid hormones and the developing hypothalamus. Eur. J. Neurosci. 32, 2096–2104.
Lesch, O.M., Dietzel, M., Musalek, M., Walter, H., Zeiler, K., 1988. The course of alcoholism. Long-term prognosis in different types. Forensic Sci. Int. 36, 121–138.
Lévesque, D., Di Paolo, T., 1991. Dopamine receptor reappearance after irreversible receptor blockade: effect of chronic estradiol treatment of ovariectomized rats. Mol. Pharmacol. 39, 659–665.
Lilley, T., Laaksonen, T., Huitu, O., Helle, S., 2010. Maternal corticosterone but not testosterone level is associated with the ratio of second-to-fourth digit length (2D:4D) in field vole offspring (Microtus agrestis). Physiol. Behav. 99, 433–437.
Lindholm, J., Fabricius-Bjerre, N., Bahnsen, M., Boiesen, P., Bangstrup, L., Pedersen, M.L., Hagen, C., 1978. Pituitary-testicular function in patients with chronic alcoholism. Eur. J. Clin. Invest. 8, 269–272.
Lindman, R.E., Koskelainen, B.M., Eriksson, C.J.P., 1999. Drinking, menstrual cycle, and female sexuality: a diary study. Alcohol. Clin. Exp. Res. 23, 169–173.
Lippa, R.A., 2006. Finger lengths, 2D:4D ratios, and their relation to gender-related personality traits and the big five. Biol. Psychol. 71, 116–121.
Little, P.J., Adams, M.L., Cicero, T.J., 1992. Effects of alcohol on the hypothalamic-pituitary-gonadal axis in the developing male rat. J. Pharmacol. Exp. Ther. 263, 1056–1061.
London, W.P., Kibbee, P., Holt, L., 1985. Handedness and alcoholism. J. Nerv. Ment. Dis. 173, 570–572.
Lovallo, W.R., Dickensheets, S.L., Myers, D.A., Thomas, T.L., Nixon, S.J., 2000. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol. Clin. Exp. Res. 24, 651–658.
Lu, S.F., McKenna, S.E., Cologer-Clifford, A., Nau, E.A., Simon, N.G., 1998. Androgen receptor in mouse brain: sex differences and similarities in autoregulation. Endocrinology 139, 1594–1601.
Luders, E., Thompson, P.M., Toga, A.W., 2010. The development of the corpus callosum in the healthy human brain. J. Neurosci. 30, 10985–10990.
Lund, E., Jacobsen, B.K., 1990. Use of oral contraceptives in relation to dietary habits and alcohol consumption. Contraception 42, 171–177.
Lutchmaya, S., Baron-Cohen, S., Raggatt, P., Knickmeyer, R., Manning, J.T., 2004. 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Hum. Dev. 77, 23–28.
Lyche, J.L., Nourizadeh-Lillabadi, R., Karlsson, C., Stavik, B., Berg, V., Skåre, J.U., Alestrøm, P., Ropstad, E., 2011. Natural mixtures of POPs affected body weight gain and induced transcription of genes involved in weight regulation and insulin signaling. Aquat. Toxicol. 102, 197–204.
Maes, M., Mommen, K., Hendrickx, D., Peeters, D., D'Hondt, P., Ranjan, R., De Meyer, F., Scharpé, S., 1997. Components of biological variation, including seasonality, in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. Clin. Endocrinol. (Oxf.) 46, 587–598.
Malas, M.A., Dogan, S., Evcil, E.H., Desdicioglu, K., 2006. Fetal development of the hand, digits and digit ratio (2D:4D). Early Hum. Dev. 82, 469–475.
Maneesh, M., Dutta, S., Chakrabarti, A., Vasudevan, D.M., 2006. Alcohol abuse-duration dependent decrease in plasma testosterone and antioxidants in males. Indian J. Physiol. Pharmacol. 50, 291–296.
Mangold, D., McCaul, M.E., Ali, M., Wand, G.S., 2000. Plasma adrenocorticotropin responses to opioid blockade with naloxone: generating a dose–response curve in a single session. Biol. Psychiatry 48, 310–314.
Mani, S.K., 2006. Signaling mechanisms in progesterone–neurotransmitter interactions. Neuroscience 138, 773–781.
Manning, J.T., 2002. Digit Ratio: A Pointer to Fertility, Behaviour and Health. Rutgers University Press, New Brunswick/New Jersey/London.
Manning, J.T., Barley, L., Walton, J., Lewis-Jones, D.I., Trivers, R.L., Singh, D., Thornhill, R., Rohde, P., Bereczkei, T., Henzi, P., Soler, M., Szwed, A., 2000a. The 2nd:4th digit ratio, sexual dimorphism, population differences, and reproductive success. evidence for sexually antagonistic genes? Evol. Hum. Behav. 21, 163–183.
Manning, J.T., Bundred, P.E., Newton, D.J., Flanagan, B.F., 2003. The second to fourth digit ratio and variation in the androgen receptor gene. Evol. Hum. Behav. 24, 399–405.
Manning, J.T., Churchill, A.J.G., Peters, M., 2007. The effects of sex, ethnicity, and sexual orientation on self-measured digit ratio (2D:4D). Arch. Sex. Behav. 36, 223–233.
Manning, J.T., Fink, B., 2011. Digit ratio, nicotine and alcohol intake and national rates of smoking and alcohol consumption. Pers. Individ. Differ. 50, 344–348.
Manning, J.T., Peters, M., 2009. Digit ratio (2D:4D) and hand preference for writing in the BBC Internet Study. Laterality 14, 528–540.
Manning, J.T., Scutt, D., Wilson, J., Lewis-Jones, D.I., 1998. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum. Reprod. 13, 3000–3004.
Manning, J.T., Stewart, A., Bundred, P.E., Trivers, R.L., 2004. Sex and ethnic differences in 2nd to 4th digit ratio of children. Early Hum. Dev. 80, 161–168.
Manning, J.T., Trivers, R.L., Thornhill, R., Singh, D., 2000b. The 2nd:4th digit ratio and asymmetry of hand performance in Jamaican children. Laterality 5, 121–132.
Manson, J.E., 2010. Pain: sex differences and implications for treatment. Metabolism. 59 (Suppl. 1), S16–S20.
Marazziti, D., Canale, D., 2004. Hormonal changes when falling in love. Psychoneuroendocrinology 29, 931–936.
Marinelli, P.W., Quirion, R., Gianoulakis, C., 2003. Estradiol valerate and alcohol intake: a comparison between Wistar and Lewis rats and the putative role of endorphins. Behav. Brain Res. 139, 59–67.
Marklein, E., Negriff, S., Dorn, L.D., 2009. Pubertal timing, friend smoking, and substance use in adolescent girls. Prev. Sci. 10, 141–150.
Marszalek, J.R., Williamson, T.L., Lee, M.K., Xu, Z., Hoffman, P.N., Becher, M.W., Crawford, T.O., Cleveland, D.W., 1996. Neurofilament subunit NF-H modulates axonal diameter by selectively slowing neurofilament transport. J. Cell Biol. 135, 711–724.
Martin, C.A., Mainous 3rd, A.G., Curry, T., Martin, D., 1999. Alcohol use in adolescent females: correlates with estradiol and testosterone. Am. J. Addict. 8, 9–14.
Martorell, R., González-Cossío, T., 1987. Maternal nutrition and birth weight. Yearb. Phys. Anthropol. 30, 195–220.
Mattila, V.M., Rimpelä, A., Jormanainen, V., Sahi, T., Pihlajamäki, H., 2010. Anabolic-androgenic steroid use among young Finnish males. Scand. J. Med. Sci. Sports 20, 330–335.
McAbee, M.D., Doncarlos, L.L., 1999. Estrogen, but not androgens, regulates androgen receptor messenger ribonucleic acid expression in the developing male rat forebrain. Endocrinology 140, 3674–3681.
McBride, W.J., Murphy, J.M., Ikemoto, S., 1999. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav. Brain Res. 101, 129–152.
McEwen, B., 2002. Estrogen actions throughout the brain. Recent Prog. Horm. Res. 57, 357–384.
McGue, M., Pickens, R.W., Svikis, D.S., 1992. Sex and age effects on the inheritance of alcohol problems: a twin study. J. Abnorm. Psychol. 101, 3–17.
McIntyre, M.H., 2006. The use of digit ratios as markers for perinatal androgen action. Reprod. Biol. Endocrinol. 4, 10.
McIntyre, M.H., Cohn, B.A., Ellison, P.T., 2006. Sex dimorphism in digital formulae of children. Am. J. Phys. Anthropol. 129, 143–150.
McIntyre, M.H., Ellison, P.T., Lieberman, D.E., Demerath, E., Towne, B., 2005. The development of sex differences in digital formula from infancy in the Fels Longitudinal Study. Proc. Biol. Sci. 272, 1473–1479.
McMechan, A.P., O'Leary-Moore, S.K., Morrison, S.D., Hannigan, J.H., 2004. Effects of prenatal alcohol exposure on forepaw digit length and digit ratios in rats. Dev. Psychobiol. 45, 251–258.
McNamara, P., Blum, D., O'Quin, K., Schachter, S., 1994. Markers of cerebral lateralization and alcoholism. Percept. Mot. Skills 79, 1435–1440.
McTiernan, A., 2008. Mechanisms linking physical activity with cancer. Nat. Rev. Cancer 8, 205–211.
Medland, S.E., Duffy, D.L., Spurdle, A.B., Wright, M.J., Geffen, G.M., Montgomery, G.W., Martin, N.G., 2005. Opposite effects of androgen receptor CAG repeat length on increased risk of left-handedness in males and females. Behav. Genet. 35, 735–744.
Medland, S.E., Duffy, D.L., Wright, M.J., Geffen, G.M., Hay, D.A., Levy, F., van-Beijsterveldt, C.E.M., Willemsen, G., Townsend, G.C., White, V., Hewitt, A.W., Mackey, D.A., Bailey, J.M., Slutske, W.S., Nyholt, D.R., Treloar, S.A., Martin, N.G., Boomsma, D.I., 2009. Genetic influences on handedness: data from 25,732 Australian and Dutch twin families. Neuropsychologia 47, 330–337.
Medland, S.E., Duffy, D.L., Wright, M.J., Geffen, G.M., Martin, N.G., 2006. Handedness in twins: joint analysis of data from 35 samples. Twin Res. Hum. Genet. 9, 46–53.
Medland, S.E., Loehlin, J.C., 2008. Multivariate genetic analyses of the 2D:4D ratio: examining the effects of hand and measurement technique in data from 757 twin families. Twin Res. Hum. Genet. 11, 335–341.
Medland, S.E., Wright, M.J., Geffen, G.M., Hay, D.A., Levy, F., Martin, N.G., Duffy, D.L., 2003. Special twin environments, genetic influences and their effects on the handedness of twins and their siblings. Twin Res. 6, 119–130.
Medland, S.E., Zayats, T., Glaser, B., Nyholt, D.R., Gordon, S.D., Wright, M.J., Montgomery, G.W., Campbell, M.J., Henders, A.K., Timpson, N.J., Peltonen, L., Wolke, D., Ring, S.M., Deloukas, P., Martin, N.G., Smith, G.D., Evans, D.M., 2010. A variant in LIN28B is associated with 2D:4D finger-length ratio, a putative retrospective biomarker of prenatal testosterone exposure. Am. J. Hum. Genet. 86, 519–525.
Mello, N.K., Bree, M.P., Mendelson, J.H., 1986. Alcohol and food self-administration by female Macaque monkeys as a function of menstrual cycle phase. Physiol. Behav. 36, 959–966.
Mello, N.K., Mendelson, J.H., Lex, B.W., 1990. Alcohol use and premenstrual symptoms in social drinkers. Psychopharmacology (Berl.) 101, 448–455.
Mendelson, J.H., Mello, N.K., Ellingboe, J., 1977. Effects of acute alcohol intake on pituitary-gonadal hormones in normal human males. J. Pharmacol. Exp. Ther. 202, 676–682.
Meriggiola, M.C., Noonan, E.A., Paulsen, C.A., Bremner, W.J., 1996. Annual patterns of luteinizing hormone, follicle stimulating hormone, testosterone and inhibin in normal men. Hum. Reprod. 11, 248–252.
Merikangas, K.R., Avenevoli, S., 2000. Implications of genetic epidemiology for the prevention of substance use disorders. Addict. Behav. 25, 807–820.
Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton, B., Zhang, H., O'Malley, S.S., Rounsaville, B.J., 1998. Familial transmission of substance use disorders. Arch. Gen. Psychiatry 55, 973–979.
Mermelstein, P.G., 2009. Membrane-localised oestrogen receptor alpha and beta influence neuronal activity through activation of metabotropic glutamate receptors. J. Neuroendocrinol. 21, 257–262.
Mermelstein, P.G., Micevych, P.E., 2008. Nervous system physiology regulated by membrane estrogen receptors. Rev. Neurosci. 19, 413–424.
Miller, W.L., 2008. Steroidogenic enzymes. Endocr. Dev. 13, 1–18.
Miller, M.A., Weafer, J., Fillmore, M.T., 2009. Gender differences in alcohol impairment of simulated driving performance and driving-related skills. Alcohol Alcohol. 44, 586–593.

Miranda, R., Ray, L., Justus, A., Meyerson, L.A., Knopik, V.S., McGeary, J., Monti, P.M., 2010. Initial evidence of an association between OPRM1 and adolescent alcohol misuse. Alcohol. Clin. Exp. Res. 34, 112–122.
Moeller, F.G., Dougherty, D.M., 2001. Antisocial personality disorder, alcohol, and aggression. Alcohol Res. Health 25, 5–11.
Moffat, S.D., Hampson, E., 1996. Salivary testosterone levels in left- and right-handed adults. Neuropsychologia 34, 225–233.
Moffat, S.D., Hampson, E., 2000. Salivary testosterone concentrations in left-handers: an association with cerebral language lateralization? Neuropsychology 14, 71–81.
Moran, L.J., Hutchison, S.K., Norman, R.J., Teede, H.J., 2011. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst. Rev. 2, CD007506.
Morissette, M., Biron, D., Di Paolo, T., 1990. Effect of estradiol and progesterone on rat striatal dopamine uptake sites. Brain Res. Bull. 25, 419–422.
Morissette, M., Di Paolo, T., 1993a. Effect of chronic estradiol and progesterone treatments of ovariectomized rats on brain dopamine uptake sites. J. Neurochem. 60, 1876–1883.
Morissette, M., Di Paolo, T., 1993b. Sex and estrous cycle variations of rat striatal dopamine uptake sites. Neuroendocrinology 58, 16–22.
Morse, J.K., DeKosky, S.T., Scheff, S.W., 1992. Neurotrophic effects of steroids on lesion-induced growth in the hippocampus. II. Hormone replacement. Exp. Neurol. 118, 47–52.
Mosselman, S., Polman, J., Dijkema, R., 1996. ER beta: identification and characterization of a novel human estrogen receptor. FEBS Lett. 392, 49–53.
Müller, C.P., Schumann, G., 2011. Drugs as instruments: a new framework for non-addictive psychoactive drug use. Behav. Brain Sci. 34, 293–310.
Müller, D.J., Likhodi, O., Heinz, A., 2010. Neural markers of genetic vulnerability to drug addiction. Curr. Top. Behav. Neurosci. 3, 277–299.
Muthusami, K.R., Chinnaswamy, P., 2005. Effect of chronic alcoholism on male fertility hormones and semen quality. Fertil. Steril. 84, 919–924.
Muti, P., Trevisan, M., Micheli, A., Krogh, V., Bolelli, G., Sciajno, R., Schünemann, H.J., Berrino, F., 1998. Alcohol consumption and total estradiol in premenopausal women. Cancer Epidemiol. Biomarkers Prev. 7, 189–193.
Nagai, M., Conney, A.H., Zhu, B.T., 2004. Strong inhibitory effects of common tea catechins and bioflavonoids on the O-methylation of catechol estrogens catalyzed by human liver cytosolic catechol-O-methyltransferase. Drug Metab. Dispos. 32, 497–504.
Nagata, C., Kabuto, M., Shimizu, H., 1998. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. Nutr. Cancer 30, 21–24.
Nakamura, K., Iwahashi, K., Furukawa, A., Ameno, K., Kinoshita, H., Ijiri, I., Sekine, Y., Suzuki, K., Iwata, Y., Minabe, Y., Mori, N., 2003. Acetaldehyde adducts in the brain of alcoholics. Arch. Toxicol. 77, 591–593.
Nasrallah, H.A., Keelor, K., McCalley-Whitters, M., 1983. Laterality shift in alcoholic males. Biol. Psychiatry 18, 1065–1067.
Nicholls, M.E.R., Orr, C.A., Yates, M.J., Loftus, A.M., 2008. A new means of measuring index/ring finger (2D:4D) ratio and its association with gender and hand preference. Laterality 13, 71–91.
Nizhnikov, M.E., Varlinskaya, E.I., Petrov, E.S., Spear, N.E., 2006. Reinforcing properties of ethanol in neonatal rats: involvement of the opioid system. Behav. Neurosci. 120, 267–280.
O'Malley, B.W., Tsai, M.J., 1992. Molecular pathways of steroid receptor action. Biol. Reprod. 46, 163–167.
O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., Rounsaville, B., 1992. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch. Gen. Psychiatry 49, 881–887.
Ogilvie, K.M., Rivier, C., 1997. Gender difference in hypothalamic-pituitary-adrenal axis response to alcohol in the rat: activational role of gonadal steroids. Brain Res. 766, 19–28.
Ökten, A., Kalyoncu, M., Yariş, N., 2002. The ratio of second- and fourth-digit lengths and congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Early Hum. Dev. 70, 47–54.
Olive, M.F., Koenig, H.N., Nannini, M.A., Hodge, C.W., 2001. Stimulation of endorphin neurotransmission in the nucleus accumbens by ethanol, cocaine, and amphetamine. J. Neurosci. 21, RC184.
Orpana, A.K., Härkönen, M., Eriksson, C.J.P., 1990. Ethanol-induced inhibition of testosterone biosynthesis in rat Leydig cells: role of mitochondrial substrate shuttles and citrate. Alcohol Alcohol. 25, 499–507.
Oswald, L.M., Wand, G.S., 2004. Opioids and alcoholism. Physiol. Behav. 81, 339–358.
Painter, R.C., De Rooij, S.R., Bossuyt, P.M.M., Osmond, C., Barker, D.J.P., Bleker, O.P., Roseboom, T.J., 2006a. A possible link between prenatal exposure to famine and breast cancer: a preliminary study. Am. J. Hum. Biol. 18, 853–856.
Painter, R.C., de Rooij, S.R., Bossuyt, P.M.M., Simmers, T.A., Osmond, C., Barker, D.J.P., Bleker, O.P., Roseboom, T.J., 2006b. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. Am. J. Clin. Nutr. 84, 322–327 quiz 466–467.
Panksepp, J.B., Lahvis, G.P., 2007. Social reward among juvenile mice. Genes Brain Behav. 6, 661–671.
Papadopoulou, N., Papakonstanti, E.A., Kallergi, G., Alevizopoulos, K., Stournaras, C., 2009. Membrane androgen receptor activation in prostate and breast tumor cells: molecular signaling and clinical impact. IUBMB Life 61, 56–61.
Papasozomenos, S.C., 1997. The heat shock-induced hyperphosphorylation of tau is estrogen-independent and prevented by androgens: implications for Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 94, 6612–6617.
Patchev, V.K., Hayashi, S., Orikasa, C., Almeida, O.F.X., 1995. Implications of estrogen-dependent brain organization for gender differences in hypothalamo-pituitary-adrenal regulation. FASEB J. 9, 419–423.
Paul, S.N., Kato, B.S., Cherkas, L.F., Andrew, T., Spector, T.D., 2006. Heritability of the second to fourth digit ratio (2d:4d): a twin study. Twin Res. Hum. Genet. 9, 215–219.
Payne, A.H., Hales, D.B., 2004. Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocr. Rev. 25, 947–970.
Pellis, S.M., 2002. Sex differences in play fighting revisited: traditional and nontraditional mechanisms of sexual differentiation in rats. Arch. Sex. Behav. 31, 17–26.
Perrin, J.S., Hervé, P.Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2008. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. J. Neurosci. 28, 9519–9524.
Peter, I., Kelley-Hedgepeth, A., Fox, C.S., Cupples, L.A., Huggins, G.S., Housman, D.E., Karas, R.H., Mendelsohn, M.E., Levy, D., Murabito, J.M., 2008. Variation in estrogen-related genes associated with cardiovascular phenotypes and circulating estradiol, testosterone, and dehydroepiandrosterone sulfate levels. J. Clin. Endocrinol. Metab. 93, 2779–2785.
Peters, K.D., Wood, R.I., 2005. Androgen dependence in hamsters: overdose, tolerance, and potential opioidergic mechanisms. Neuroscience 130, 971–981.
Peters, M., Reimers, S., Manning, J.T., 2006. Hand preference for writing and associations with selected demographic and behavioral variables in 255,100 subjects: the BBC internet study. Brain Cogn. 62, 177–189.
Pfannkuche, K.A., Bouma, A., Groothuis, T.G.G., 2009. Does testosterone affect lateralization of brain and behaviour? A meta-analysis in humans and other animal species. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 364, 929–942.
Pfaus, J.G., Wilkins, M.F., Dipietro, N., Benibgui, M., Toledano, R., Rowe, A., Couch, M.C., 2010. Inhibitory and disinhibitory effects of psychomotor stimulants and depressants on the sexual behavior of male and female rats. Horm. Behav. 58, 163–176.
Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369–382.
Piazza, P.V., Deroche, V., Deminière, J.M., Maccari, S., Le Moal, M., Simon, H., 1993. Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. Proc. Natl. Acad. Sci. U. S. A. 90, 11738–11742.
Pierucci-Lagha, A., Covault, J., Feinn, R., Nellissery, M., Hernandez-Avila, C., Oncken, C., Morrow, A.L., Kranzler, H.R., 2005. GABRA2 alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. Neuropsychopharmacology 30, 1193–1203.
Pirnik, Z., Schwendt, M., Jezova, D., 2001. Single dose of morphine influences plasma corticosterone and gene expression of main NMDA receptor subunit in the adrenal gland but not in the hippocampus. Endocr. Regul. 35, 187–193.
Pluchino, N., Merlini, S., Cubeddu, A., Giannini, A., Bucci, F., Casarosa, E., Cela, V., Angioni, S., Luisi, M., Genazzani, A.R., 2009a. Brain-region responsiveness to DT56a (Femarelle) administration on allopregnanolone and opioid content in ovariectomized rats. Menopause 16, 1037–1043.
Pluchino, N., Ninni, F., Casarosa, E., Giannini, A., Merlini, S., Cubeddu, A., Luisi, M., Cela, V., Genazzani, A.R., 2009b. Sex differences in brain and plasma beta-endorphin content following testosterone, dihydrotestosterone and estradiol administration to gonadectomized rats. Neuroendocrinology 89, 411–423.
Poikolainen, K., 2000. Risk factors for alcohol dependence: a case–control study. Alcohol Alcohol. 35, 190–196.
Pope Jr., H.G., Kouri, E.M., Hudson, J.I., 2000. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. Arch. Gen. Psychiatry 57, 133–140 discussion 155–156.
Porrino, L.J., Lyons, D., Smith, H.R., Daunais, J.B., Nader, M.A., 2004. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. J. Neurosci. 24, 3554–3562.
Potenza, M.N., de Wit, H., 2010. Control yourself: alcohol and impulsivity. Alcohol. Clin. Exp. Res. 34, 1303–1305.
Prasad, C., Prasad, A., 1995. A relationship between increased voluntary alcohol preference and basal hypercorticosteronemia associated with an attenuated rise in corticosterone output during stress. Alcohol 12, 59–63.
Prendergast, M.A., 2004. Do women possess a unique susceptibility to the neurotoxic effects of alcohol? J. Am. Med. Wom. Assoc. 59, 225–227.
Prichard, Z., Jorm, A.F., Prior, M., Sanson, A., Smart, D., Zhang, Y., Huttley, G., Easteal, S., 2002. Association of polymorphisms of the estrogen receptor gene with anxiety-related traits in children and adolescents: a longitudinal study. Am. J. Med. Genet. 114, 169–176.
Prichard, Z.M., Jorm, A.F., Mackinnon, A., Easteal, S., 2007. Association analysis of 15 polymorphisms within 10 candidate genes for antisocial behavioural traits. Psychiatr. Genet. 17, 299–303.
Primus, R.J., Kellogg, C.K., 1991. Gonadal status and pubertal age influence the responsiveness of the benzodiazepine/GABA receptor complex to environmental challenge in male rats. Brain Res. 561, 299–306.
Proverbio, A.M., Brignone, V., Matarazzo, S., Del Zotto, M., Zani, A., 2006. Gender differences in hemispheric asymmetry for face processing. BMC Neurosci. 7, 44.
Pulkkinen, L., Pitkänen, T., 1994. A prospective study of the precursors to problem drinking in young adulthood. J. Stud. Alcohol 55, 578–587.
Purohit, V., 1998. Moderate alcohol consumption and estrogen levels in postmenopausal women: a review. Alcohol. Clin. Exp. Res. 22, 994–997.
Purohit, V., 2000. Can alcohol promote aromatization of androgens to estrogens? A review. Alcohol 22, 123–127.

Quinones-Jenab, V., Jenab, S., 2010. Progesterone attenuates cocaine-induced responses. Horm. Behav. 58, 22–32.
Rajagopal, A., Vassilopoulou-Sellin, R., Palmer, J.L., Kaur, G., Bruera, E., 2003. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. J. Pain Symptom Manage. 26, 1055–1061.
Ramlau-Hansen, C.H., Thulstrup, A.M., Olsen, J., Ernst, E., Andersen, C.Y., Bonde, J.P., 2008. Maternal smoking in pregnancy and reproductive hormones in adult sons. Int. J. Androl. 31, 565–572.
Rasmussen, D.D., Bryant, C.A., Boldt, B.M., Colasurdo, E.A., Levin, N., Wilkinson, C.W., 1998. Acute alcohol effects on opiomelanocortinergic regulation. Alcohol. Clin. Exp. Res. 22, 789–801.
Ren, F., Zhang, S., Mitchell, S.H., Butler, R., Young, C.Y.F., 2000. Tea polyphenols down-regulate the expression of the androgen receptor in LNCaP prostate cancer cells. Oncogene 19, 1924–1932.
Rivier, C., 1999. Alcohol rapidly lowers plasma testosterone levels in the rat: evidence that a neural brain–gonadal pathway may be important for decreased testicular responsiveness to gonadotropin. Alcohol. Clin. Exp. Res. 23, 38–45.
Rivier, C., Rivest, S., 1991. Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms. Biol. Reprod. 45, 523–532.
Roberts, A.J., Gold, L.H., Polis, I., McDonald, J.S., Filliol, D., Kieffer, B.L., Koob, G.F., 2001. Increased ethanol self-administration in delta-opioid receptor knockout mice. Alcohol. Clin. Exp. Res. 25, 1249–1256.
Roberts, A.J., Smith, A.D., Weiss, F., Rivier, C., Koob, G.F., 1998. Estrous cycle effects on operant responding for ethanol in female rats. Alcohol. Clin. Exp. Res. 22, 1564–1569.
Roberts, L.J., Finch, P.M., Pullan, P.T., Bhagat, C.I., Price, L.M., 2002. Sex hormone suppression by intrathecal opioids: a prospective study. Clin. J. Pain 18, 144–148.
Robertson, J., Zhang, W., Liu, J.J., Muir, K.R., Maciewicz, R.A., Doherty, M., 2008. Radiographic assessment of the index to ring finger ratio (2D:4D) in adults. J. Anat. 212, 42–48.
Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18, 247–291.
Robinson, T.E., Berridge, K.C., 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95 (Suppl. 2), S91–S117.
Roche, D.J.O., Childs, E., Epstein, A.M., King, A.C., 2010. Acute HPA axis response to naltrexone differs in female vs. male smokers. Psychoneuroendocrinology 35, 596–606.
Roepke, T.A., Qiu, J., Bosch, M.A., Rønnekleiv, O.K., Kelly, M.J., 2009. Cross-talk between membrane-initiated and nuclear-initiated oestrogen signalling in the hypothalamus. J. Neuroendocrinol. 21, 263–270.
Romeo, R.D., Staub, D., Jasnow, A.M., Karatsoreos, I.N., Thornton, J.E., McEwen, B.S., 2005. Dihydrotestosterone increases hippocampal N-methyl-D-aspartate binding but does not affect choline acetyltransferase cell number in the forebrain or choline transporter levels in the CA1 region of adult male rats. Endocrinology 146, 2091–2097.
Rose, R.J., 1998. A developmental behavior—genetic perspective on alcoholism risk. Alcohol Health Res. World 22, 131–143.
Rösner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., Soyka, M., 2010. Opioid antagonists for alcohol dependence. Cochrane Database Syst. Rev. CD001867.
Rupprecht, R., Holsboer, F., 1999a. Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. Trends Neurosci. 22, 410–416.
Rupprecht, R., Holsboer, F., 1999b. Neuropsychopharmacological properties of neuroactive steroids. Steroids 64, 83–91.
Ruusa, J., Bergman, B., 1996. Sex hormones and alcohol withdrawal: does a good supply of testosterone prevent serious symptoms during detoxification? Alcohol 13, 139–145.
Sachser, N., Hennessy, M.B., Kaiser, S., 2011. Adaptive modulation of behavioural profiles by social stress during early phases of life and adolescence. Neurosci. Biobehav. Rev. 35, 1518–1533.
Sandberg, D., David, S., Stewart, J., 1982. Effects of estradiol benzoate on the pattern of eating and ethanol consumption. Physiol. Behav. 29, 61–65.
Sandberg, D., Stewart, J., 1982. Effects of estradiol benzoate and MER-25 on ethanol consumption in the ovariectomized rat. J. Comp. Physiol. Psychol. 96, 635–648.
Sarkar, P., Bergman, K., O'Connor, T.G., Glover, V., 2008. Maternal antenatal anxiety and amniotic fluid cortisol and testosterone: possible implications for foetal programming. J. Neuroendocrinol. 20, 489–496.
Sarkola, T., Eriksson, C.J.P., 2003. Testosterone increases in men after a low dose of alcohol. Alcohol. Clin. Exp. Res. 27, 682–685.
Sarkola, T., Fukunaga, T., Mäkisalo, H., Eriksson, C.J.P., 2000. Acute effect of alcohol on androgens in premenopausal women. Alcohol Alcohol. 35, 84–90.
Sartippour, M.R., Pietras, R., Marquez-Garban, D.C., Chen, H.W., Heber, D., Henning, S.M., Sartippour, G., Zhang, L., Lu, M., Weinberg, O., Rao, J.Y., Brooks, M.N., 2006. The combination of green tea and tamoxifen is effective against breast cancer. Carcinogenesis 27, 2424–2433.
Sarton, E., Olofsen, E., Romberg, R., den Hartigh, J., Kest, B., Nieuwenhuijs, D., Burm, A., Teppema, L., Dahan, A., 2000. Sex differences in morphine analgesia: an experimental study in healthy volunteers. Anesthesiology 93, 1245–1254 discussion 1246A.
Satoh, K., Sakamoto, Y., Ogata, A., Nagai, F., Mikuriya, H., Numazawa, M., Yamada, K., Aoki, N., 2002. Inhibition of aromatase activity by green tea extract catechins and their endocrinological effects of oral administration in rats. Food Chem. Toxicol. 40, 925–933.
Satz, P., Green, M.F., 1999. Atypical handedness in schizophrenia: some methodological and theoretical issues. Schizophr. Bull. 25, 63–78.
Scaramuzzo, R.T., Boldrini, A., Bertelloni, S., Parrini, D., Serino, L., Ghirri, P., 2010. Low testosterone levels in pre-term newborns born small for gestational age. J. Endocrinol. Invest. 33, 215–217.
Schäfer, I., Teske, L., Schulze-Thüsing, J., Homann, K., Reimer, J., Haasen, C., Hissbach, J., Wiedemann, K., 2010. Impact of childhood trauma on hypothalamus-pituitary-adrenal axis activity in alcohol-dependent patients. Eur. Addict. Res. 16, 108–114.
Schonfeld, A.M., Mattson, S.N., Riley, E.P., 2005. Moral maturity and delinquency after prenatal alcohol exposure. J. Stud. Alcohol 66, 545–554.
Schuckit, M.A., Irwin, M., 1989. An analysis of the clinical relevance of type 1 and type 2 alcoholics. Br. J. Addict. 84, 869–876.
Schulte, M.T., Ramo, D., Brown, S.A., 2009. Gender differences in factors influencing alcohol use and drinking progression among adolescents. Clin. Psychol. Rev. 29, 535–547.
Schulz, K.M., Molenda-Figueira, H.A., Sisk, C.L., 2009a. Back to the future: the organizational-activational hypothesis adapted to puberty and adolescence. Horm. Behav. 55, 597–604.
Schulz, K.M., Richardson, H.N., Zehr, J.L., Osetek, A.J., Menard, T.A., Sisk, C.L., 2004. Gonadal hormones masculinize and defeminize reproductive behaviors during puberty in the male Syrian hamster. Horm. Behav. 45, 242–249.
Schulz, K.M., Zehr, J.L., Salas-Ramirez, K.Y., Sisk, C.L., 2009b. Testosterone programs adult social behavior before and during, but not after, adolescence. Endocrinology 150, 3690–3698.
Sholl, S.A., Kim, K.L., 1990. Androgen receptors are differentially distributed between right and left cerebral hemispheres of the fetal male rhesus monkey. Brain Res. 516, 122–126.
Shrenker, P., Maxson, S.C., Ginsburg, B.E., 1985. The role of postnatal testosterone in the development of sexually dimorphic behaviors in DBA/1Bg mice. Physiol. Behav. 35, 757–762.
Shrubsole, M.J., Lu, W., Chen, Z., Shu, X.O., Zheng, Y., Dai, Q., Cai, Q., Gu, K., Ruan, Z.X., Gao, Y.T., Zheng, W., 2009. Drinking green tea modestly reduces breast cancer risk. J. Nutr. 139, 310–316.
Shughrue, P.J., Lane, M.V., Merchenthaler, I., 1997. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. J. Comp. Neurol. 388, 507–525.
Silveri, M.M., Spear, L.P., 2004. Characterizing the ontogeny of ethanol-associated increases in corticosterone. Alcohol 32, 145–155.
Singh, K., Prasad, S., 2008. Age- and sex-related analysis of methylation of 5′-upstream sequences of Fmr-1 gene in mouse brain and modulation by sex steroid hormones. Biogerontology 9, 455–465.
Sisk, C.L., Zehr, J.L., 2005. Pubertal hormones organize the adolescent brain and behavior. Front. Neuroendocrinol. 26, 163–174.
Sjöberg, R.L., Ducci, F., Barr, C.S., Newman, T.K., Dell'osso, L., Virkkunen, M., Goldman, D., 2008. A non-additive interaction of a functional *MAO*-A VNTR and testosterone predicts antisocial behavior. Neuropsychopharmacology 33, 425–430.
Sluyter, F., Hof, M., Ellenbroek, B.A., Degen, S.B., Cools, A.R., 2000. Genetic, sex, and early environmental effects on the voluntary alcohol intake in Wistar rats. Pharmacol. Biochem. Behav. 67, 801–808.
Soler, H., Vinayak, P., Quadagno, D., 2000. Biosocial aspects of domestic violence. Psychoneuroendocrinology 25, 721–739.
Spanagel, R., 2009. Alcoholism: a systems approach from molecular physiology to addictive behavior. Physiol. Rev. 89, 649–705.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463.
Sperling, W., Biermann, T., Bleich, S., Galvin, R., Maihöfner, C., Kornhuber, J., Reulbach, U., 2010. Non-right-handedness and free serum testosterone levels in detoxified patients with alcohol dependence. Alcohol Alcohol. 45, 237–240.
Sperling, W., Frank, H., Martus, P., Mader, R., Barocka, A., Walter, H., Lesch, M., 2000. The concept of abnormal hemispheric organization in addiction research. Alcohol Alcohol. 35, 394–399.
Stacey, D., Clarke, T.K., Schumann, G., 2009. The genetics of alcoholism. Curr. Psychiatry Rep. 11, 364–369.
Stoyanov, Z., Marinov, M., Pashalieva, I., 2009. Finger length ratio (2D:4D) in left- and right-handed males. Int. J. Neurosci. 119, 1006–1013.
Stromberg, M.F., Casale, M., Volpicelli, L., Volpicelli, J.R., O'Brien, C.P., 1998. A comparison of the effects of the opioid antagonists naltrexone, naltrindole, and beta-funaltrexamine on ethanol consumption in the rat. Alcohol 15, 281–289.
Strong, M.N., Yoneyama, N., Fretwell, A.M., Snelling, C., Tanchuck, M.A., Finn, D.A., 2010. "Binge" drinking experience in adolescent mice shows sex differences and elevated ethanol intake in adulthood. Horm. Behav. 58, 82–90.
Stumpf, W.E., Sar, M., 1976. Steroid hormone target sites in the brain: the differential distribution of estrogin, progestin, androgen and glucocorticosteroid. J. Steroid Biochem. 7, 1163–1170.
Sulzer, D., 2011. How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron 69, 628–649.
Sun, Y., Xun, K., Wang, C., Zhao, H., Bi, H., Chen, X., Wang, Y., 2009. Adiponectin, an unlocking adipocytokine. Cardiovasc. Ther. 27, 59–75.
Susser, E., Hoek, H.W., Brown, A., 1998. Neurodevelopmental disorders after prenatal famine: the story of the Dutch Famine Study. Am. J. Epidemiol. 147, 213–216.
Sutker, P.B., Libet, J.M., Allain, A.N., Randall, C.L., 1983. Alcohol use, negative mood states, and menstrual cycle phases. Alcohol. Clin. Exp. Res. 7, 327–331.

Suzuki, R., Allen, N.E., Appleby, P.N., Key, T.J., Dossus, L., Tjønneland, A., Føns Johnsen, N., Overvad, K., Sacerdote, C., Palli, D., Krogh, V., Tumino, R., Rohrmann, S., Linseisen, J., Boeing, H., Trichopoulou, A., Makrygiannis, G., Misirli, G., Bueno-de-Mesquita, H.B., May, A.M., Díaz, M.J., Sánchez, M.J., Barricarte Gurrea, A., Rodríguez Suárez, L., Buckland, G., Larrañaga, N., Bingham, S., Khaw, K.T., Rinaldi, S., Slimani, N., Jenab, M., Riboli, E., Kaaks, R., 2009. Lifestyle factors and serum androgens among 636 middle aged men from seven countries in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 20, 811–821.

Talarovicová, A., Krsková, L., Blazeková, J., 2009. Testosterone enhancement during pregnancy influences the 2D:4D ratio and open field motor activity of rat siblings in adulthood. Horm. Behav. 55, 235–239.

Tambour, S., Brown, L.L., Crabbe, J.C., 2008. Gender and age at drinking onset affect voluntary alcohol consumption but neither the alcohol deprivation effect nor the response to stress in mice. Alcohol. Clin. Exp. Res. 32, 2100–2106.

Tan, Ü., 1991. Serum testosterone levels in male and female subjects with standard and anomalous dominance. Int. J. Neurosci. 58, 211–214.

Tan, Ü., 1992. Testosterone and estradiol in right-handed men but only estradiol in right-handed women is inversely correlated with the degree of right-hand preference. Int. J. Neurosci. 66, 25–34.

Tan, Ü., 2008. Ratio of fourth to second fingertip extensions in relation to serum estradiol and testosterone levels in men and women. Percept. Mot. Skills 107, 3–13.

Tan, Ü., Tan, M., 2001. Testosterone and grasp-reflex differences in human neonates. Laterality 6, 181–192.

Tennant, F., Black, D.L., Voy, R.O., 1988. Anabolic steroid dependence with opioid-type features. N. Engl. J. Med. 319, 578.

Thiblin, I., Lindquist, O., Rajs, J., 2000. Cause and manner of death among users of anabolic androgenic steroids. J. Forensic Sci. 45, 16–23.

Travison, T.G., Araujo, A.B., Kupelian, V., O'Donnell, A.B., McKinlay, J.B., 2007. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J. Clin. Endocrinol. Metab. 92, 549–555.

Travison, T.G., Shackelton, R., Araujo, A.B., Morley, J.E., Williams, R.E., Clark, R.V., McKinlay, J.B., 2010. Frailty, serum androgens, and the CAG repeat polymorphism: results from the Massachusetts Male Aging Study. J. Clin. Endocrinol. Metab. 95, 2746–2754.

Treutlein, J., Cichon, S., Ridinger, M., Wodarz, N., Soyka, M., Zill, P., Maier, W., Moessner, R., Gaebel, W., Dahmen, N., Fehr, C., Scherbaum, N., Steffens, M., Ludwig, K.U., Frank, J., Wichmann, H.E., Schreiber, S., Dragano, N., Sommer, W.H., Leonardi-Essmann, F., Lourdusamy, A., Gebicke-Haerter, P., Wienker, T.F., Sullivan, P.F., Nöthen, M.M., Kiefer, F., Spanagel, R., Mann, K., Rietschel, M., 2009. Genome-wide association study of alcohol dependence. Arch. Gen. Psychiatry. 66, 773–784.

Trigo, J.M., Martin-García, E., Berrendero, F., Robledo, P., Maldonado, R., 2010. The endogenous opioid system: a common substrate in drug addiction. Drug Alcohol Depend. 108, 183–194.

Tschann, J.M., Adler, N.E., Irwin Jr., C.E., Millstein, S.G., Turner, R.A., Kegeles, S.M., 1994. Initiation of substance use in early adolescence: the roles of pubertal timing and emotional distress. Health Psychol. 13, 326–333.

Turgeon, J.L., Waring, D.W., 2000. Progesterone regulation of the progesterone receptor in rat gonadotropes. Endocrinology 141, 3422–3429.

Uhart, M., Chong, R.Y., Oswald, L., Lin, P.I., Wand, G.S., 2006. Gender differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity. Psychoneuroendocrinology 31, 642–652.

Uht, R.M., Anderson, C.M., Webb, P., Kushner, P.J., 1997. Transcriptional activities of estrogen and glucocorticoid receptors are functionally integrated at the AP-1 response element. Endocrinology 138, 2900–2908.

Umathe, S.N., Bhutada, P.S., Dixit, P.V., Jain, N.S., 2008. Leuprolide: a luteinizing hormone releasing hormone agonist attenuates ethanol withdrawal syndrome and ethanol-induced locomotor sensitization in mice. Neuropeptides 42, 345–353.

Urban, N.B.L., Kegeles, L.S., Slifstein, M., Xu, X., Martinez, D., Sakr, E., Castillo, F., Moadel, T., O'Malley, S.S., Krystal, J.H., Abi-Dargham, A., 2010. Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [(1)(1)C]raclopride. Biol. Psychiatry 68, 689–696.

Välimäki, M., Pelkonen, R., Härkönen, M., Ylikahri, R., 1984. Hormonal changes in noncirrhotic male alcoholics during ethanol withdrawal. Alcohol Alcohol. 19, 235–242.

van Anders, S.M., Goldey, K.L., 2010. Testosterone and partnering are linked via relationship status for women and 'relationship orientation' for men. Horm. Behav. 58, 820–826.

van Anders, S.M., Vernon, P.A., Wilbur, C.J., 2006. Finger-length ratios show evidence of prenatal hormone-transfer between opposite-sex twins. Horm. Behav. 49, 315–319.

van Anders, S.M., Watson, N.V., 2006. Relationship status and testosterone in North American heterosexual and non-heterosexual men and women: cross-sectional and longitudinal data. Psychoneuroendocrinology 31, 715–723.

Van Thiel, D.H., Gavaler, J.S., Cobb, C.F., Santucci, L., Graham, T.O., 1983. Ethanol, a Leydig cell toxin: evidence obtained in vivo and in vitro. Pharmacol. Biochem. Behav. 18 (Suppl. 1), 317–323.

Van Thiel, D.H., Gavaler, J.S., Rosenblum, E., Eagon, P.K., 1987. Effects of ethanol on endocrine cells: testicular effects. Ann. N. Y. Acad. Sci. 492, 287–302.

Van Waes, V., Enache, M., Berton, O., Vinner, E., Lhermitte, M., Maccari, S., Darnaudéry, M., 2011. Effect of prenatal stress on alcohol preference and sensitivity to chronic alcohol exposure in male rats. Psychopharmacology (Berl). 214, 197–208.

Vanbillemont, G., Lapauw, B., Bogaert, V., De Naeyer, H., De Bacquer, D., Ruige, J., Kaufman, J.M., Taes, Y.E.C., 2010. Birth weight in relation to sex steroid status and body composition in young healthy male siblings. J. Clin. Endocrinol. Metab. 95, 1587–1594.

Vardavas, C.I., Chatzi, L., Patelarou, E., Plana, E., Sarri, K., Kafatos, A., Koutis, A.D., Kogevinas, M., 2010. Smoking and smoking cessation during early pregnancy and its effect on adverse pregnancy outcomes and fetal growth. Eur. J. Pediatr. 169, 741–748.

Varlinskaya, E.I., Spear, L.P., 2002. Acute effects of ethanol on social behavior of adolescent and adult rats: role of familiarity of the test situation. Alcohol. Clin. Exp. Res. 26, 1502–1511.

Varlinskaya, E.I., Spear, L.P., 2004. Acute ethanol withdrawal (hangover) and social behavior in adolescent and adult male and female Sprague-Dawley rats. Alcohol. Clin. Exp. Res. 28, 40–50.

Varlinskaya, E.I., Spear, L.P., 2006. Differences in the social consequences of ethanol emerge during the course of adolescence in rats: social facilitation, social inhibition, and anxiolysis. Dev. Psychobiol. 48, 146–161.

Varlinskaya, E.I., Spear, L.P., 2009. Ethanol-induced social facilitation in adolescent rats: role of endogenous activity at mu opioid receptors. Alcohol. Clin. Exp. Res. 33, 991–1000.

Vermeulen, A., Verdonck, L., Kaufman, J.M., 1999. A critical evaluation of simple methods for the estimation of free testosterone in serum. J. Clin. Endocrinol. Metab. 84, 3666–3672.

Vescovi, P.P., DiGennaro, C., Coiro, V., 1997. Hormonal (ACTH, cortisol, beta-endorphin, and met-enkephalin) and cardiovascular responses to hyperthermic stress in chronic alcoholics. Alcohol. Clin. Exp. Res. 21, 1195–1198.

Viau, V., 2002. Functional cross-talk between the hypothalamic-pituitary-gonadal and -adrenal axes. J. Neuroendocrinol. 14, 506–513.

Virkkunen, M., Rawlings, R., Tokola, R., Poland, R.E., Guidotti, A., Nemeroff, C., Bissette, G., Kalogeras, K., Karonen, S.L., Linnoila, M., 1994. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Arch. Gen. Psychiatry 51, 20–27.

Volpicelli, J.R., Alterman, A.I., Hayashida, M., O'Brien, C.P., 1992. Naltrexone in the treatment of alcohol dependence. Arch. Gen. Psychiatry 49, 876–880.

von der Pahlen, B., Sarkola, T., Seppä, K., Eriksson, C.J.P., 2002. Testosterone, 5 alpha-dihydrotestosterone and cortisol in men with and without alcohol-related aggression. J. Stud. Alcohol 63, 518–526.

Voracek, M., Dressler, S.G., 2007. Digit ratio (2D:4D) in twins: heritability estimates and evidence for a masculinized trait expression in women from opposite-sex pairs. Psychol. Rep. 100, 115–126.

Voracek, M., Reimer, B., Ertl, C., Dressler, S.G., 2006. Digit ratio (2D:4D), lateral preferences, and performance in fencing. Percept. Mot. Skills 103, 427–446.

Vuoksimaa, E., Eriksson, C.J.P., Pulkkinen, L., Rose, R.J., Kaprio, J., 2010. Decreased prevalence of left-handedness among females with male co-twins: evidence suggesting prenatal testosterone transfer in humans? Psychoneuroendocrinology 35, 1462–1472.

Vuoksimaa, E., Koskenvuo, M., Rose, R.J., Kaprio, J., 2009. Origins of handedness: a nationwide study of 30,161 adults. Neuropsychologia 47, 1294–1301.

Wallen, K., 2009. Does finger fat produce sex differences in second to fourth digit ratios? Endocrinology 150, 4819–4822.

Walter, M., Gerhard, U., Gerlach, M., Weijers, H.G., Boening, J., Wiesbeck, G.A., 2007. Controlled study on the combined effect of alcohol and tobacco smoking on testosterone in alcohol-dependent men. Alcohol Alcohol. 42, 19–23.

Walter, P., Green, S., Greene, G., Krust, A., Bornert, J.M., Jeltsch, J.M., Staub, A., Jensen, E., Scrace, G., Waterfield, M., Chambon, P., 1985. Cloning of the human estrogen receptor cDNA. Proc. Natl. Acad. Sci. U. S. A. 82, 7889–7893.

Wand, G.S., Dobs, A.S., 1991. Alterations in the hypothalamic-pituitary-adrenal axis in actively drinking alcoholics. J. Clin. Endocrinol. Metab. 72, 1290–1295.

Weaver, I.C.G., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854.

Weber, E., Martin, R., Voigt, K.H., 1979. Corticotropin/beta-endorphin precursor: concomitant storage of its fragments in the secretory granules of anterior pituitary corticotropin/endorphin cells. Life Sci. 25, 1111–1118.

Weinberg, J., Sliwowska, J.H., Lan, N., Hellemans, K.G.C., 2008. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J. Neuroendocrinol. 20, 470–488.

Westberg, L., Baghaei, F., Rosmond, R., Hellstrand, M., Landén, M., Jansson, M., Holm, G., Björntorp, P., Eriksson, E., 2001. Polymorphisms of the androgen receptor gene and the estrogen receptor beta gene are associated with androgen levels in women. J. Clin. Endocrinol. Metab. 86, 2562–2568.

WHO, 2011. Global Status Report on Alcohol and Health. http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf, accessed: 28 May 2011.

Wilsnack, R.W., Wilsnack, S.C., Klassen, A.D., 1984. Women's drinking and drinking problems: patterns from a 1981 national survey. Am. J. Public Health 74, 1231–1238.

Wilsnack, S.C., Wilsnack, R.W., 2002. International gender and alcohol research: recent findings and future directions. Alcohol Res. Health 26, 245–250.

Wilson, D.M., Killen, J.D., Hayward, C., Robinson, T.N., Hammer, L.D., Kraemer, H.C., Varady, A., Taylor, C.B., 1994. Timing and rate of sexual maturation and the onset of cigarette and alcohol use among teenage girls. Arch. Pediatr. Adolesc. Med. 148, 789–795.

Wines Jr., J.D., Gruber, A.J., Pope Jr., H.G., Lukas, S.E., 1999. Nalbuphine hydrochloride dependence in anabolic steroid users. Am. J. Addict. 8, 161–164.
Winslow, J.T., Miczek, K.A., 1988. Androgen dependency of alcohol effects on aggressive behavior: a seasonal rhythm in high-ranking squirrel monkeys. Psychopharmacology (Berl.) 95, 92–98.
Wise, R.A., 2002. Brain reward circuitry: insights from unsensed incentives. Neuron 36, 229–240.
Wise, R.A., 2004. Dopamine, learning and motivation. Nat. Rev. Neurosci. 5, 483–494.
Witelson, S.F., 1985. The brain connection: the corpus callosum is larger in left-handers. Science 229, 665–668.
Witelson, S.F., 1991. Neural sexual mosaicism: sexual differentiation of the human temporo-parietal region for functional asymmetry. Psychoneuroendocrinology 16, 131–153.
Witelson, S.F., Nowakowski, R.S., 1991. Left out axons make men right: a hypothesis for the origin of handedness and functional asymmetry. Neuropsychologia 29, 327–333.
Witt, E.D., 2007. Puberty, hormones, and sex differences in alcohol abuse and dependence. Neurotoxicol. Teratol. 29, 81–95.
Wood, R.I., 2006. Anabolic steroids: a fatal attraction? J. Neuroendocrinol. 18, 227–228.
Wu, A.H., Arakawa, K., Stanczyk, F.Z., Van Den Berg, D., Koh, W.P., Yu, M.C., 2005. Tea and circulating estrogen levels in postmenopausal Chinese women in Singapore. Carcinogenesis 26, 976–980.
Wu, A.H., Butler, L.M., 2011. Green tea and breast cancer. Mol. Nutr. Food Res. 55, 921–930.
Wu, F.C.W., Tajar, A., Pye, S.R., Silman, A.J., Finn, J.D., O'Neill, T.W., Bartfai, G., Casanueva, F., Forti, G., Giwercman, A., Huhtaniemi, I.T., Kula, K., Punab, M., Boonen, S., Vanderschueren, D., 2008. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J. Clin. Endocrinol. Metab. 93, 2737–2745.
Wurst, F.M., Rasmussen, D.D., Hillemacher, T., Kraus, T., Ramskogler, K., Lesch, O., Bayerlein, K., Schanze, A., Wilhelm, J., Junghanns, K., Schulte, T., Dammann, G., Pridzun, L., Wiesbeck, G., Kornhuber, J., Bleich, S., 2007. Alcoholism, craving, and hormones: the role of leptin, ghrelin, prolactin, and the pro-opiomelanocortin system in modulating ethanol intake. Alcohol. Clin. Exp. Res. 31, 1963–1967.
Xiao, C., Shao, X.M., Olive, M.F., Griffin 3rd, W.C., Li, K.Y., Krnjević, K., Zhou, C., Ye, J.H., 2009. Ethanol facilitates glutamatergic transmission to dopamine neurons in the ventral tegmental area. Neuropsychopharmacology 34, 307–318.
Xiao, C., Ye, J.H., 2008. Ethanol dually modulates GABAergic synaptic transmission onto dopaminergic neurons in ventral tegmental area: role of mu-opioid receptors. Neuroscience 153, 240–248.
Xiao, L., Jordan, C.L., 2002. Sex differences, laterality, and hormonal regulation of androgen receptor immunoreactivity in rat hippocampus. Horm. Behav. 42, 327–336.
Yeap, B.B., Almeida, O.P., Hyde, Z., Norman, P.E., Chubb, S.A.P., Jamrozik, K., Hankey, G.J., Flicker, L., 2009. Healthier lifestyle predicts higher circulating testosterone in older men: the Health In Men Study. Clin. Endocrinol. (Oxf.) 70, 455–463.
Young, S.E., Corley, R.P., Stallings, M.C., Rhee, S.H., Crowley, T.J., Hewitt, J.K., 2002. Substance use, abuse and dependence in adolescence: prevalence, symptom profiles and correlates. Drug Alcohol Depend. 68, 309–322.
Ypsilanti, A., Ganou, M., Koidou, I., Grouios, G., 2008. Digit ratio (2D:4D) in individuals with intellectual disability: investigating the role of testosterone in the establishment of cerebral lateralisation. Laterality 13, 527–544.
Zacny, J.P., 2001. Morphine responses in humans: a retrospective analysis of sex differences. Drug Alcohol Depend. 63, 23–28.
Zhang, M., Huang, J., Xie, X., Holman, C.D.J., 2009. Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. Int. J. Cancer 124, 1404–1408.
Zheng, P., 2009. Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. Prog. Neurobiol. 89, 134–152.
Zheng, Z., Cohn, M.J., 2011. Developmental basis of sexually dimorphic digit ratios. Proc. Natl. Acad. Sci. U. S. A. 108, 16289–16294.
Zhou, L., Hammer Jr., R.P., 1995. Gonadal steroid hormones upregulate medial preoptic mu-opioid receptors in the rat. Eur. J. Pharmacol. 278, 271–274.
Zitzmann, M., Nieschlag, E., 2001. Testosterone levels in healthy men and the relation to behavioural and physical characteristics: facts and constructs. Eur. J. Endocrinol. 144, 183–197.
Zuckermann, M., Buchsbaum, M.S., Murphy, D.L., 1980. Sensation seeking and its biological correlates. Psychol. Bull. 88, 187–214.