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Polydrug Use in Adolescence

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1. Introduction

1.1 Drug and polydrug use among adolescents

The 2010 Monitoring the Future survey conducted by the US government raises concerns about an increase in drug use among teenagers, particularly those of a younger age. A similar trend has been reflected by European surveys, such as the 2010 Annual report on the state of the drugs problem in Europe, EMCDDA. According to this study, commissioned by the European Council, the use of multiple substances – polydrug use – is widespread and represents a major challenge. A recent survey by the Spanish government (EDADES 2009/2010) revealed that approximately 50% of drug users consumed two or more substances simultaneously. The objective of users is to increase or reverse the effects of the different drugs taken, but greater health risks and problems and a poor treatment response are also inherent in polydrug consumption. Almost all patterns of polydrug use include alcohol, and the use of amphetamines or ecstasy among frequent or heavy alcohol consumers is much higher than the average. A study by the Spanish government (Encuesta Estatal sobre uso de drogas en estudiantes de enseñanzas secundarias, ESTUDES, 2008) revealed that Spanish students between 14-18 years old who used drugs generally consumed more than one drug at the same time. 96.2% of students who had taken ecstasy in the previous year had simultaneously consumed alcohol and 86.1% had simultaneously consumed cannabis. An association between consumption of stimulants and hallucinogen drugs was also reported. For example, among students who had used ecstasy in the previous year, 71.4% had also consumed cocaine, while 38.5% of those who had used cocaine in the same period had also consumed ecstasy.

2. The adolescent brain

Adolescence is the period of gradual physiological, cognitive, behavioural and psychosocial transition from childhood to adulthood (Pickles et al., 1998) during which individuals experience physical changes, new interests, greater independence and heightened responsibility. Since adolescence is a process, it is difficult to characterize its ontogenetic time course, and no single event signals its onset or termination. In humans, adolescence is often considered to begin with the onset of the biological changes associated with puberty (the period during which an individual becomes sexually mature), although the timing of puberty within the adolescent period varies notably among humans. Adolescence ends when the individual assumes adult social roles, with a change in the sleep pattern having

been proposed as a physiological marker of its termination (Abbott, 2005). The adolescent age span in humans is commonly considered to be from 12 to 18 years, although the entire second decade is sometimes considered adolescence, with up to 25 years being considered late adolescence (Baumrind, 1987).

Adolescent subjects exhibit certain characteristic behaviours (some of which are common among adolescents across species), including hyperphagia, shorter periods of sleep, increases in peer-directed social interactions and affiliation with peers, an increase in the number of conflicts with parents, egocentrism, a lack of 'common sense' in decision-making, rigidity in reasoning, impulsivity, including a preference for actions that offer immediate rewards (cognitive impulsivity), reduced self-control, enhanced novelty-seeking and risk-taking behaviours (Spear, 2011a; Sturman & Moghaddam, 2011). All of these behaviours can lead to a higher incidence of risky behaviours such as misconduct at school, drink driving, unsafe sex, use of illegal drugs, and antisocial behaviours (Doremus-Fitzwater et al., 2010; Eaton et al., 2010; Spear, 2011b). Although cognitive control improves throughout adolescence (Luna et al., 2010), youths show differences in cognitive strategies in relation to adults. According to the "fuzzy trace theory" adolescents process the risk and benefits of choices more explicitly than adults, which, paradoxically, leads to greater risk-taking (Rivers et al., 2008). The characteristic irresponsibility of adolescents may be due to differences in the way in which they experience risk and reward, especially under conditions of heightened emotional arousal (Sturman & Moghaddam, 2011). Thus, the risk-taking behaviour of adolescents is probably related to the fact that their decision-making capacity is more vulnerable to disruption by stress. Adolescence is generally considered to be a stressful stage of life, and individuals are more likely to perceive events as stressful at this age, with adolescents exhibiting higher rates of depressed mood, sleep problems, emotional instability, anxiety and self-consciousness (Buchanan et al., 1992). Moreover, some aspects of neurobehavioural and hormonal responses to stressors also vary when adolescents are compared to younger or older individuals (Allen & Matthews, 1997). Similarly, behavioural experiments in laboratory animals have revealed that adolescents are more disrupted by stressors than younger or older counterparts and that they differ behaviourally and physiologically in their response to stressors when compared to animals of other ages (Buwalda et al., 2011; Stone & Quartermain, 1998; Vázquez, 1998). For example, the rise in plasma corticosterone levels induced by restraint stress is prolonged in adolescent rats in comparison with adult animals. Moreover, while adult male rats, which are repeatedly exposed to daily restraint stress, show a clear habituation in their neuroendocrine response, adolescent male rats actually exhibit a facilitation of this response (Romeo, 2010).

The characteristic behaviour of adolescence can be explained in neurobiological terms (Brenhouse & Andersen, 2011; Casey et al., 2011; Sturman & Moghaddam, 2011). Indeed, the features of an adolescent brain predispose individuals to behaving in the way referred to above. Maturation alterations of the brain contribute to these age-specific behavioural characteristics, including the increase in risk-taking and propensity to use drugs of abuse (Doremus-Fitzwater et al., 2010). Recent research has demonstrated the importance of gonadal hormones for neurobehavioural maturation during adolescence in laboratory animals and an association between gonadal hormones and adolescent behaviour/mood in humans (see Vigil et al., 2011, for review). Adolescence represents a stage of development of the nervous system (as does embryonic development) in which steroid hormones trigger various organizational phenomena related to structural brain circuit remodelling:

myelination, apoptosis, neural pruning, and dendritic spine remodelling, thus determining the adult behavioural response to steroids or sensory stimuli (Vigil et al., 2011).

The adolescent brain undergoes dramatic changes in gross morphology. During this phase there is a massive loss of gray matter and synapses in neocortical brain regions (Gogtay et al., 2004), and the most characteristic ontogenetic change, which occurs across a variety of species, is an alteration of the prefrontal cortex. Throughout human adolescence there is a marked increase in hemispheric asymmetry and in the degree to which the two cerebral hemispheres can process information independently (Merola & Liederman, 1985). In the primate cortex, the density of receptors of different neurotransmitter systems (dopamine, serotonin, acetylcholine, and GABA) decreases as adolescence progresses (Lidow et al., 1991; Brenhouse & Andersen, 2011). Most of the synapses that undergo pruning during adolescence are excitatory, which results in a decline in N-methyl-D-aspartate (NMDA) receptors and the extension of glutaminergic excitatory stimulation to the cortex (Insel et al., 1990). There is a body of evidence to show that the balance of excitatory and inhibitory neurotransmission varies between adolescents and adults, suggesting that the increased inhibition associated with development of the prefrontal cortex promotes greater neural coordination (Sturman & Moghaddam, 2011).

Maturation changes are also evident during adolescence in limbic regions such as the hippocampus (Insel et al., 1990; Wolfer and Lipp, 1995), and gray matter reductions also take place in the striatum and other subcortical structures (Sowell et al., 2002). Conversely, white matter increases in cortical and subcortical fiber tracts (Paus et al., 2001) and in circuits connecting the amygdala and striatum with the prefrontal cortex (Asato et al. 2010). A decrease is observed in glutamate receptors in the hippocampus (Insel et al., 1990) and DA receptors in the striatum (Seeman et al., 1987; Teicher et al., 1995). Cannabinoid binding peaks in the limbic forebrain of rats during adolescence before declining to adult levels (Rodriguez de Fonseca et al., 1993). Experimental evidence supports a shift during adolescence from a relative balance between subcortical and cortical DA systems toward a greater predominance of cortical DA. In contrast to this enhanced DA tone in the prefrontal cortex during adolescence, DA activity in the accumbens and other subcortical DA terminal regions seems to be less noticeable in adolescents than in adults (Andersen & Gazzara, 1993). Basal levels of synaptic DA are lower during this phase of development, although adolescents show a greater and faster increase in drug-induced DA release (Badanich et al. 2006; Laviola et al. 2001). Consistent with this, adolescents are generally subject to a less positive impact from stimuli with moderate to low incentive value, and thus seek additional appetitive reinforcers (Spear, 2000).

Neuroimaging studies have shown variations in human adolescent functional activity in different forebrain regions, including the amygdala, orbitofrontal cortex and striatum (Bjork et al., 2010). For example, the amygdala and accumbens of adolescents exhibit more activity than those of adults (Ernst et al., 2002). Similarly, in comparison to adults, adolescents show a lower response to reward in the lateral orbitofrontal cortex and a higher activity in the nucleus accumbens (Galvan et al., 2006). Neural coordination within and between brain regions as well as processing efficiency are reduced in adolescents due to a less-effective information transfer between regions, incomplete myelination, and imbalances in neuronal inhibition/excitation within critical brain regions (Sturman & Moghaddam, 2011). Human and animal studies have revealed a differential development of subcortical limbic systems related to top-down control systems during adolescent brain development, with subcortical

limbic systems developing earlier than control systems. It has been proposed that the mechanisms underlying adolescent changes in behaviour (impulsiveness, risky choices, drug taking, etc.) could underlie an imbalance between an increased sensitivity to motivational cues and immature cognitive control (Casey et al., 2011). In summary, immature neuronal processing in the prefrontal cortex and other cortical and subcortical regions, and their interaction, lead to a behaviour that is biased toward risk and emotional reactivity during the adolescent period (Sturman & Moghaddan, 2011).

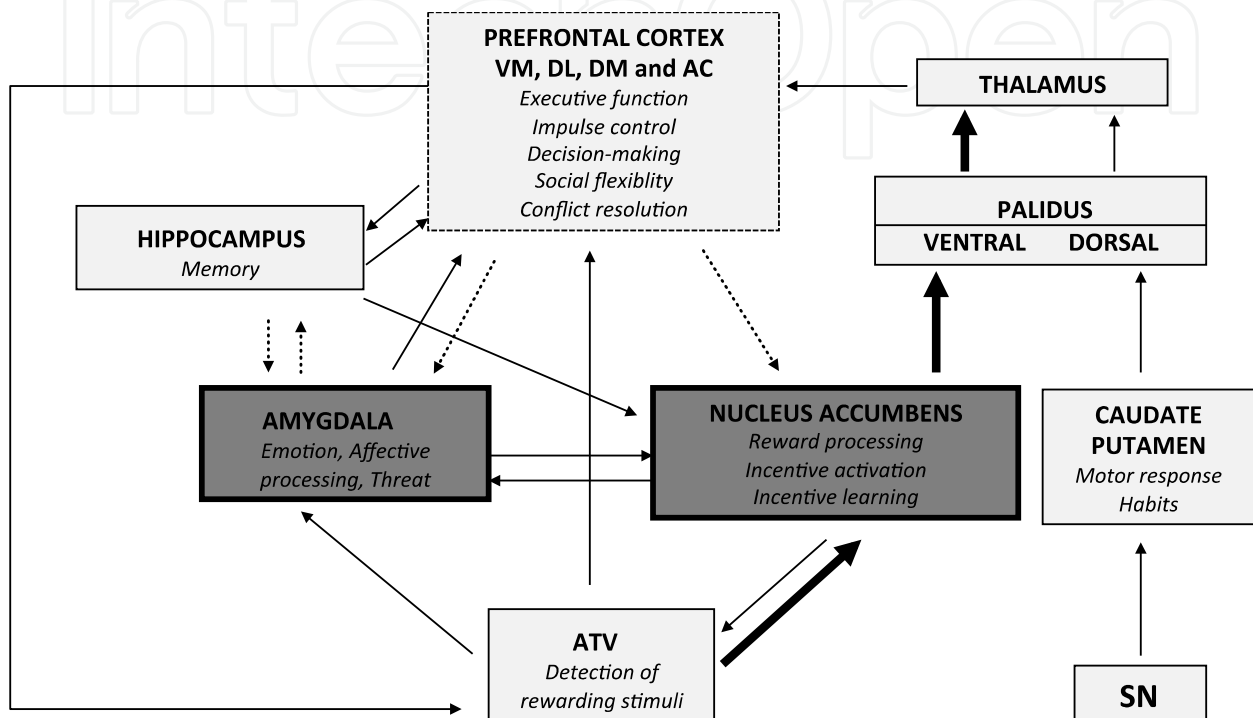


Fig. 1. Neural circuit involved in motivated behaviour. Thick lines represent hyperactive brain areas or connections and faint and dashed lines represent brain areas that are more hypoactive in adolescent subjects than in adults.

The adolescent brain operates in a promotivational state due to the combination of three factors:

- limited inhibitory capacity and poor regulatory control (due to the lack of cortical maturation)
- DA hyperactivity in the nucleus accumbens when processing appetitive stimuli
- Amygdala hyperactivity, which explains affective intensity and liability, and a weaker harm-avoidance system (Ernst et al., 2009).

The relatively early development of bottom-up limbic regions (nucleus accumbens and amygdala), along with an immaturity of top-down regulatory systems (PFC), biases behavior toward risk-taking, risk-seeking, impulsive choice, sensation-seeking and novelty preference.

3. Effects of drugs on adolescents

In addition to increases in sensation- and novelty-seeking, drug use is more common during adolescence (2010 Annual report on the state of the drugs problem in Europe, EMCDDA;

Doremus-Fitzwater et al., 2010; Spear, 2011b). Youngsters differ from adults in their response to a variety of drugs (Schramm-Sapyta et al., 2009). These ontogenetic variations in drug responsiveness may be related with age differences in pharmacokinetics, particularly with respect to the functioning of the neural substrates upon which these drugs act, and also with social enhancement. As discussed previously, the neural systems involved in the effects exerted by drugs (mesolimbic DA system) differ considerably between adolescents and adults. These ontogenetic differences in drug responsiveness may have significant consequences for adolescents, who exhibit a reduced sensitivity to various drugs of abuse. This insensitivity can promote greater use per occasion in relation to more mature individuals (Schramm-Sapyta et al., 2009). After peer substance use, the next most powerful predictor of adolescent alcohol and drug use is perceived stress (Wagner et al., 1999). In animal models, stress has been shown to increase the rewarding effects of drugs of abuse (Piazza & LeMoal, 1998; Ribeiro Do Couto et al., 2006). On the other hand, experimental data suggest that drugs of abuse induce stronger effects in adolescents than in adults, although the literature is not conclusive regarding these differences (for review see Schramm-Sapyta et al., 2009). The developmental stage of adolescence can promote early experimentation with drugs, as addictive substances are generally more rewarding and less aversive (Schramm-Sapyta et al., 2009).

Moreover, adolescent substance use disrupts the normal development of an adolescent brain. Exposure to drugs of abuse can induce neurobehavioural, neurochemical and neuroendocrinal effects in the adolescent rat brain, thereby affecting the growth process and systems involved in plasticity and cognition (Jain & Balhara, 2010). Since adolescents undergo structural and functional dynamic changes in brain areas implicated in the reinforcing properties of drugs of abuse (prefrontal cortex and ventral striatum) and habit formation (dorsal striatum), drug-taking during this period could increase susceptibility to drug dependence, although there is a lack of studies that demonstrate causality.

4. Animal models of drug addiction

The use of animal models to study drug addiction has the advantage of experimental control of variables (age of initial exposure, drug, dose, duration, timing of exposure, etc.) and has provided much valuable information. The main drawback to animal studies is that no model completely reproduces all the stages in the development of drug addiction. Results obtained with multiple behavioural and neurobiological models are necessary to achieve a deeper understanding of this disorder (Ahmed, 2010; Belin et al. 2010; Sanchis-Segura & Spanagel, 2006; Schramm-Sapyta et al., 2009; Shippenberg & Koob, 2002; Weiss, 2010).

There are several animal models with a high predictive value, though most studies are performed with one of two paradigms: self-administration or conditioned place preference (CPP) (Aguilar et al., 2009). The most direct procedure for evaluating the reinforcing properties of a substance is self-administration (the animal works to obtain the substance: for example by pressing a lever), which assesses the intrinsic rewarding properties of a substance; and both oral and intravenous routes have been used to assess the relevance of age in voluntary intake. Animals that acquire drug-taking behaviour more quickly or indulge in it more frequently can be considered to resemble human drug addicts. However, drug taking, even when acquired quickly, is not equivalent to drug dependence (Ahmed, 2010). Another shortcoming of the self-administration paradigm is the complexity of the

technique and the lack of a standardized procedure for evaluating substances with different potencies, reinforcement properties and pharmacokinetics. The choice of training substance, species and procedural parameters can radically affect the results obtained (Moser et al., 2011). Variations of the self-administration model have been developed to study the main features of addiction. For example, the progressive ratio method designed by Hodos (1961), in which the sweetness and volume of a milk is varied in order to measure reward strength, has been used to assess motivation to seek a drug (Depoortere et al., 1993). On the other hand, extinction and reinstatement paradigms are employed to model relapse. Following acquisition of self-administration, animals undergo a process by which the response is extinguished and reinstatement is induced by drug priming, stress or drug-associated cues (Shaham et al., 2003; Epstein et al., 2006). Time-out and punished responding model compulsive use (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004) and long-access training schedules model high-level use (Knackstedt & Kalivas, 2007). Additionally, models of habitual drug-seeking have also been developed (Everitt et al., 2008).

The CPP paradigm (in which rodents repeatedly exposed to a distinct environment in the presence of a positively reinforcing substance show preference for that environment) evaluates the conditioned rewarding properties of a substance, and is also frequently used due to its procedural simplicity and rapidity. This model is dose-sensitive, and drugs of abuse are typically rewarding at low to moderate doses and aversive at high doses. CPP is sensitive to a wide range of substances. In general, CPP is useful for measuring the level and persistence of drug-induced reward (Tzschentke, 1998), but not for modelling pathological drug-seeking or taking. For this reason, variations of this procedure (adding an extinction and reinstatement of the extinguished conditioned preference) have been developed to model addiction-like behaviours (Aguilar et al., 2009).

Other animal models are employed to study motor behaviour, conditioned aversion, withdrawal, sensitization and compulsive drug-seeking (Belin et al., 2009; Schramm-Sapyta et al., 2009; Weiss, 2010). Most drugs of abuse stimulate locomotor behaviour through activation of the dopaminergic circuits that contribute to their reinforcing effects. At lower doses locomotor activity is generally increased, whereas at higher doses, locomotion falls and stereotypical behaviour can emerge. Conditioned place and taste aversion are designed to assess the aversive effects of drugs of abuse (which are assumed to discourage intake). Animals are trained to associate a place or a palatable flavour with the aversive sensations induced by a drug injected by the experimenter (generally lithium), which causes the place or flavour to be subsequently avoided. These tests measure the use-limiting effects of drugs of abuse but do not model pathological drug-seeking or taking (Schramm-Sapyta et al., 2009), since experimenter-delivered injections greatly differ from volitional intake even for the aversive effects of the drug (Galici et al., 2000).

Withdrawal is a constellation of affective and physiological changes that occurs after cessation of intake of some drugs of abuse and is used to evaluate dependence. Symptoms generally reflect the reversal of initial drug effects, although they vary with the drug, duration and extent of exposure. This, together with the kind of observations made and the choice of end points, can obstruct the interpretation of withdrawal effects (Moser et al., 2011). In the case of ethanol or opioids, withdrawal effects (including autonomic and behavioural activation) can be easily quantified in animal models. Withdrawal from psychostimulants and most other drugs of abuse results in a generalized “negative

motivational state" which can be assessed using an intracranial self-stimulation procedure (Bauzo & Bruijnzeel, 2012) or an anxiety-like state which can be assessed using many models, including the social interaction test and elevated plus maze (Hall et al. 2010). Repeated exposure to any of the aforementioned drugs can lead to a phenomenon called sensitization, in which the ambulatory, stereotypic or rewarding effect of a repeated low dose is augmented. Sensitization reflects lasting neuroplastic changes in response to repeated exposure, and is hypothesized to be a behavioural correlate of increased drug craving and development of dependence (Robinson and Berridge, 2008), though its relevance to drug dependence is debatable. However, since data from sensitization studies have led to the development of pharmacotherapies that have been tested in animal models of relapse and in human addicts, some authors support sensitisation as a useful model for determining the neural basis of addiction (Steketee & Kalivas, 2011). Compulsive drug-seeking is analysed by the more complex methods of self-administration (progressive ratio, extinction, reinstatement, punishment, long-access, etc.), which tend to be more informative regarding vulnerability to addiction. However, it is difficult to employ these new techniques in developmental studies that aim to examine the behaviour of adolescent vs adult rodents, partly due to the prolonged duration of the experimental procedures.

5. Animal models of adolescent polydrug consumption

Recent advances in imaging have made it easier to study the human brain, but many questions about the effect of drugs in the adolescent brain require experimental manipulation in experimental animals in order to be answered. Given the across-species similarities in neurobehavioural features of adolescence, non-human animals undergoing this developmental transition can be used as models of human adolescence (Spear, 2000). There is growing evidence that adolescent humans and rodents experience many similar structural and functional changes in the brain as they progress towards adulthood. Behavioural changes characteristic of adolescence (increased social behaviour, novelty- and sensation-seeking, risk-taking, emotional instability and impulsivity) are also observed in rodents (Jain & Balhara, 2010). However, the use of adolescent rodent models does have some limitations. There are numerous areas of adolescent functioning in humans that cannot be addressed using animal models (peer pressure and self esteem, impact of parenting styles, obsession about weight, etc.). Moreover, the increases in adrenal hormones/neuroactive steroids during adrenarche in humans are generally not evident in other mammalian species. Furthermore, forebrain systems of rodents are less prominent than in humans, their social organization is simpler, and the time course of adolescence is briefer. The time frame of adolescence in non-human animals such as the rat is even more difficult to characterize than in humans. Among researchers who study adolescence in rats, opinions differ somewhat (Spear, 2000). The problem is further magnified by the limited amount of research to have focused on adolescence in laboratory animals. Animals of both genders exhibit neurobehavioural characteristics typical of adolescence during the period between postnatal days 28 and 42. According to hormonal, physical and social criteria, this development phase corresponds with age 12-18 in humans (Spear 2000). Moreover, different physiological changes (growth spurt, loss of excitatory input to prefrontal cortex, vaginal opening in females and increases in maturing spermatids in males) occur during this period. Indeed, some ontogenetic changes that signal the early onset of adolescence in female rats can emerge as early as 20 days of age, with later development taking place up until 55-60

days of age in males. Taking into account the abovementioned limitations, adolescent rodent models can be considered to possess good face and construct validity, since there are strong similarities between human adolescents and various animal models of adolescence in terms of developmental history, behavioural traits and neural and hormonal characteristics (Spear, 2011a). As more information is generated, stronger evidence of these forms of validity, and of predictive validity, will no doubt be obtained.

Moreover, there are several methodological difficulties that are encountered when using experimental animals to model the complex pattern of drug abuse observed in humans. A polydrug animal model of drug abuse allows a situation that is closer to reality than the simple effect produced by one drug. However, a number of variables need to be taken into account when using such a model. Comparison of the studies published in the literature is difficult, since practically each one of them represents a different model of polydrug administration. This is to be expected given the high number of variables involved in this kind of study (Schensul et al., 2005). The first variable to bear in mind is the combination of drugs employed. In most studies only two drugs are employed; in many cases cocaine or alcohol. Another important aspect is the temporal pattern of drug administration employed. Until now, most studies have focused on acute administration (Braidia & Sala, 2002; Daza-Losada et al., 2009a; Diller et al., 2007; Manzanedo et al., 2010; Robledo et al., 2007), though there is a growing number of studies employing repeated administration and studying long-term effects (Achat-Mendes et al., 2003; Daza-Losada et al., 2008a, 2008b, 2009; Estelles et al., 2006; Jones et al., 2010; Ribeiro Do Couto et al., 2011a, 2011b; Rodriguez-Arias et al., 2011). This is another point of discrepancy; some studies have measured effects after very short periods post-administration (only 2 or 3 days), while others have assessed effects weeks or even months after the last administration. Finally, the effect under evaluation can vary considerably between purely physiological studies and those focusing exclusively on behavioural changes. All these discrepancies point to the fact that polydrug models simplify the complex reality of human consumption, in which each the pattern of drug use of each individual is unique.

Most of the studies that have assessed polydrug use have employed adult animals and acute administration. Thus, it is necessary to design models of adolescent polydrug consumption that reflect the human reality, despite the intrinsic difficulties they may pose. Our research group has been working for several years in this field during which we have studied different drug combinations and different patterns of drug administration.

The aim of the present chapter is to offer a detailed review of the experiments performed in this area. With this purpose in mind we will discuss not only the key results obtained in our experiments but also those of other studies of adolescent polydrug use. In an attempt to provide a clear overview of the evidence obtained to date, studies have been classified according to the pattern of drug administration employed. In this way, studies employing acute administration of drugs and studying immediate effects have been grouped together. Studies evaluating the binge pattern of drug administration, commonly employed by users of psychostimulants, constitute a second group. This section also represents a recently employed model developed with the aim of replicating the binge drinking that is so common among adolescents and young people of many cultures. Finally, we will discuss several studies in which a specific drug has triggered the reinstatement of drug-seeking behaviour of a different pharmacological kind of drug, known as the cross-reinstatement phenomenon and also the phenomenon of sensitization.

6. Principal results

6.1 Acute polydrug studies

6.1.1 MDMA plus cocaine

Preclinical studies have until now focused mainly on the long-term consequences of drug pre-treatment in terms of subsequent changes in spontaneous behaviour or in the response to other drugs of abuse. For instance, a substantial number of studies have focused on the long-term consequences of MDMA pre-treatment on subsequent cocaine administration (Achat-Mendes et al., 2003; Åberg et al., 2007; Daza-Losada et al., 2008, 2009b). However, hardly any have examined the interactive profile of concomitant exposure to MDMA and cocaine. Diller and coworkers (2007) studied the effects of concurrent administration of MDMA and cocaine on CPP in adult rats, finding that both drugs induced CPP when administered alone. Co-administration, on the other hand, produced an antagonism, except when higher doses were employed. These results highlight how the neurochemical and behavioural effects of MDMA and cocaine consumed separately are dramatically altered when taken together. Based on the inverse relation between serotonin and DA activity (in general, decreases in serotonin neurotransmission produce an increase of DA function) (Di Giovanni et al., 2010), these authors speculated that cocaine had undermined MDMA-mediated serotonin release more than MDMA-mediated DA release, thereby increasing the overall reward.

In a more recent study, we focused on the interaction of acute MDMA and cocaine administration in adolescent mice (Daza-Losada et al., 2009a), studying the acute interaction of both drugs on motor activity, anxiety, memory and brain monoamines. One of the most important results of this study was that acutely administered cocaine plus MDMA induced an anxiolytic response in the elevated plus maze that was not present when the drugs were administered separately. Mice treated with cocaine and MDMA spent significantly more time in the open arms of the plus maze than controls or animals treated with just one of the drugs. This result was not due to an unspecific increase of motor activity, as no increase in the number of total or closed entries was observed in animals treated with both drugs. Although numerous studies have indicated that MDMA causes anxiety problems in drug users (for review see Baylen et al., 2006), our results revealed that MDMA alone does not exert a strong effect on levels of anxiety in adolescent mice. The few studies performed in the plus maze with mice have shown that acute MDMA administration induces anxiogenic or anxiolytic effects that vary depending on the dose employed (Navarro et al. 2002). Although all the available evidence supports an anxiogenic effect of acute cocaine administration in adult mice (Erhardt et al., 2006), cocaine did not affect the behaviours studied in the plus maze in our study. One possible explanation could be the different experimental conditions of the studies compared or a different dose-response curve to cocaine in adolescent versus adult mice. These results endorse the hypothesis that adolescent animals are more “protected” from adverse psychostimulant-related properties than older subjects (Laviola et al., 1999), and highlight the importance of employing adolescent animals in studies.

Another important observation of our study was that an increase in DA turnover in the striatum was observed only when both drugs were administered together, due to a substantial increase in DOPAC concentration that was not accompanied by alterations of

DA levels. Neither serotonin nor its metabolites were altered in the striatum, but there was an increase in the concentration of serotonin in the cortex (total cortex, including the frontal cortex), which led to a decrease in its turnover. Although MDMA and cocaine act on the same neurotransmitter systems, the mechanisms involved differ, as do the effects produced. MDMA provokes an acute release of both serotonin and dopamine from nerve terminals (review in Colado et al., 2004) and is more potent in inhibiting serotonin and norepinephrine than dopamine transporters, while cocaine blocks these three monoamine transporters at similar concentrations (Han et al., 2006). One report suggested that serotonin plays a more prominent role in the psychotropic effects of MDMA than in those of cocaine (Itzhak et al., 2006). As in our study, both drugs were administered together, cocaine appeared to block MDMA entry into the nerve terminals, thereby inhibiting MDMA-mediated monoamine release, which mainly affects serotonin. On the other hand, the reuptake-blocking effects of these compounds may have been an added factor that made DA more available to the synapse, which could have been responsible for the increase in dopaminergic turnover observed. This DA/serotonergic balance, which occurred only in the groups treated with both drugs, could be, in part, responsible for the anxiolytic effect observed when cocaine and MDMA were administered together. Our results endorse the hypothesis of Diller and coworkers (2007), since we have observed an increase in DA turnover and lower levels of serotonin turnover in the striatum and cortex. These findings point to an increase in DA availability in conjunction with the release of serotonin in small amounts or at a slow rate, leading to a decrease in its turnover. These studies demonstrate that the combined use of MDMA and cocaine produces a specific neurochemical and behavioural profile different to that observed when each drug is administered alone.

6.1.2 MDMA plus cannabinoids

Several studies have highlighted that the prolonged combined use of MDMA and cannabis is associated with a variety of psychological problems, including elevated impulsiveness, anxiety and psychotic behaviour (Daumann et al., 2004). The cannabinoid system interacts with a variety of neurotransmitters, including DA and serotonin (Nakazi et al., 2000), and represents a common neurobiological substrate for the addictive properties of different drugs of abuse (Maldonado et al., 2006). In line with this, many of the physiological responses provoked by MDMA are modulated by the endocannabinoid system (Piomelli et al., 2005).

Few studies have clarified the effects of exposure to cannabinoids on liability to MDMA abuse, and most of them suggest that cannabinoid agonists potentiate the rewarding effects of MDMA (Braida & Sala, 2002). However, studies performed recently have demonstrated that cannabinoid agonists modify sensitivity to the behavioural effects of MDMA in different ways (increase/decrease) depending on the dose employed. We have observed that a low dose of the specific CB1 agonist WIN 55212-2 increases the rewarding effects of an ineffective dose of MDMA administered during acquisition of the CPP. However, higher doses of the cannabinoid agonist weaken the preference induced by effective doses of MDMA (Manzanedo et al., 2010). Our results are in accordance with those of Robledo and co-workers (2007), who reported that a sub-threshold dose of THC produced CPP in mice when combined with a non-rewarding dose of MDMA but decreased the CPP induced by an effective dose of MDMA.

Cannabinoids participate in the regulation of DA synthesis, release and turnover (Gardner et al., 1998). The overlapping expression of cannabinoid and dopamine receptors in some brain areas such as the nucleus accumbens (Hermann et al., 2002) may represent a neuroanatomical substrate for such an interaction. At doses that neither WIN 55212-2 nor MDMA alter brain monoamines, animals treated with both drugs exhibited decreases of striatal DA and serotonin in the cortex (Manzanedo et al., 2010). Despite the anti-inflammatory and anti-oxidative properties of cannabinoids (Pazos et al., 2008; Aggarwal et al., 2009), animal studies have revealed that chronic administration of THC causes hippocampal damage (Fisk et al., 2006) and that exposure to low concentrations of cannabinoids over a prolonged period is likely to have a neurotoxic effect (Rubovitch et al., 2002; Sarne & Keren, 2004). This evidence points to the capacity of cannabinoids to increase the neurotoxic potential of MDMA. We must keep in mind that, due to the crucial role that the DA system plays in the reinforcing effects of drugs of abuse, the neurotoxic effect of MDMA on mice could modulate the response of lesioned brains to these drugs. For instance, mice pre-exposed to neurotoxic doses of MDMA exhibit a higher consumption of, and a preference for, EtOH than saline-treated animals (Izco et al. 2007).

6.2 Binge pattern

6.2.1 MDMA plus cocaine

Epidemiological data reveal that the majority of MDMA users cease taking the drug spontaneously in their twenties (von Sydow et al., 2002), which highlights the relevance of using adolescent subjects in animal models. In addition to presenting a distinctive behavioural profile (Spear, 2000; Adriani & Laviola, 2003), young rats and mice are highly sensitive to the administration of psychostimulant agents (Laviola et al., 1999; Spear, 2000).

Both MDMA and cocaine have been proved to induce long-term response after their consumption. MDMA users present weeks after discontinuation of intake, a reduced hormonal response to drug challenge and a combination of depressive pattern, dysphoria, high levels of aggressiveness and elevated scores of novelty-seeking behaviour (Gerra et al., 1998). These long-term effects have also been described in mice and rats exposed to MDMA during adolescence, among which changes in social behaviour (Morley-Fletcher et al., 2002), motor activity (Balogh et al., 2004) and anxiety levels (Faria et al., 2006; Clemens et al., 2007) have been detected. On the other hand, cocaine administration also induces long-term effects in adolescent mice, which are expressed through increased flee and avoidance behaviour and fewer social contacts (Estelles et al., 2006). However, the long-lasting effect of the combination of two drugs taken during adolescence has received little attention. Furthermore, it should be taken into consideration that human MDMA and cocaine consumers commonly adhere to a binge pattern, which has been associated with a higher occurrence of stimulant-induced psychosis and addiction (Gawin, 1991; Segal & Kuczenski, 1997; Belin et al., 2011). To explore these effects, we performed a series of studies using a model that mimics a binge pattern of MDMA and cocaine consumption. This model consists of two daily injections (at 8 am and 8 pm) of an identical dose of MDMA alone or plus cocaine, for 3 days (6 administrations), between postnatal day 28 and 30. Mice were evaluated three weeks after the last treatment, on postnatal day 51. MDMA administration decreased the concentration of striatal DA when administered at high doses (20 mg/kg) in agreement with previous reports (for review see Colado et al., 2004), but cocaine inhibited

this decrease in DA concentration three weeks later (Daza-Losada et al., 2008a). In accordance with these results, pretreatment with the dopamine uptake inhibitor GBR 12909 prevented long-term loss in the striatal concentration of DA (O'Shea et al., 2001). This lack of neurotoxicity could have been due to the effect exerted on body temperature by the two drugs together, as cocaine is known to counteract the increase produced by neurotoxic doses of MDMA. Most evidence suggests that merely preventing MDMA-induced hyperthermia is enough to produce significant neuroprotection (Colado et al., 2001). Although a rise in temperature is an important element in MDMA-induced neurotoxicity, this phenomenon appears to involve more than MDMA metabolites, including dopamine deamination and/or autooxidation (Sprague & Nichols, 2005). As we administered both drugs together, it is also feasible that cocaine interfered with the dopamine uptake system by inhibiting the entry of MDMA into the nerve terminal. By affecting one or several of these processes, cocaine is capable of blocking dopamine neurodegeneration in the mouse brain.

Since many MDMA users employ opiates in order to relieve the psychostimulant effects of ecstasy, it is of relevance to evaluate whether such individuals are subject to an increase in the well-known rewarding properties of morphine. We have observed that, following MDMA binges during adolescence, sensitivity to reinstatement of an extinguished preference is increased, as a morphine-induced preference was reinstated with lower priming doses in MDMA-treated mice than in non-treated animals (Daza-Losada et al., 2008b). In the literature regarding learning, reinstatement refers to the recovery of a learned response when a subject is non-contingently exposed to either a conditioned or an unconditioned stimulus after extinction. This recovery of a learned response, which represents a return to drug seeking, occurs when rats or mice are exposed to drugs, drug cues or stressors following extinction. In the CPP version of the reinstatement model, an extinguished CPP is robustly reinstated by non-contingent administration of a priming dose of the drug (Aguilar et al., 2009). Contrasting results were obtained when adolescent mice were treated with cocaine alone or plus MDMA. These animals need higher priming doses of morphine than non-treated mice in order to reinstate the preference. The ability of repeated treatment with psychomotor stimulants to enhance the response to subsequent challenge by an opiate seems to be affected by the route and timing of administration of each drug. Prenatal treatment with cocaine decreases the rewarding actions of morphine in adult offspring (Estelles et al., 2006), while, in adult rats, doses of morphine that fail to produce CPP have been shown to induce a marked preference in those which have previously received cocaine (Shippenberg et al., 1998). However, when acute challenge with heroin takes place 3 weeks after daily systemic injections of cocaine, locomotor cross-sensitization does not occur (DeVries et al., 1998). When cocaine is administered during gestational development, the development of brain reward systems can be altered, resulting in a long-term attenuation of the rewarding properties of morphine. Nevertheless, the possibility that such animals are unable to form the necessary association between a particular environment and morphine cannot be ruled out (Heyser et al., 1990; Inman-Wood et al., 2000). Additionally, prenatal exposure to cocaine can reduce the duration of pregnancy, gestational weight gain and food intake in the dams, factors that can contribute to an abnormal response to morphine. Finally, an association between prenatal cocaine exposure and the effect of altered maternal behaviour on later cognitive functions cannot be ruled out.

Thus, MDMA-treated mice are more vulnerable to relapse after receiving a priming administration of morphine, but this tendency is completely blocked in animals exposed to cocaine, in which an opposite effect is exhibited. Cocaine induces modifications in DA receptor function and transduction events mainly in the mesocorticolimbic dopamine pathway, where it induces an up-regulation of the cAMP-signalling pathway (Nestler, 2004) and augments the activity of the transcription factor cAMP response element-binding protein (CREB) (Walters et al., 2003). Increased CREB expression in the nucleus accumbens undermines the rewarding effects of both cocaine (Carlezon et al., 1998) and morphine (Barrot et al., 2002). In addition, repeated exposure to cocaine upregulates DYN/KOPr systems (Shippenberg et al., 2007). This increase may initially serve as a homeostatic response that opposes the alteration in neurotransmission that occurs after exposure to this drug use. However, following the discontinuation of drug use, the unopposed actions of this system are likely to result in dysregulation of basal DA and glutamate transmission, thereby contributing to aberrant activity within the prefrontal-cortico-striatal loop (Shippenberg et al., 2007). These could represent some of the mechanisms responsible for the way in which cocaine affects the response of the dopaminergic system by altering the intensity of the response to priming.

MDMA and cocaine are often first consumed at an early age, and the response to MDMA of users in their twenties can be affected by previous exposure to these or other drugs. Similarly to the observations reported with morphine, Achat-Mendes and co-workers (2003) found that a priming injection of cocaine after extinction reinstated a significantly higher CPP in mice previously exposed during adolescence to a comparable regimen of MDMA. Comparable results have been described in adolescent (Aberg et al., 2007) and adult rats (Horan et al., 2000). These results are also in accordance with the finding that the acquisition of cocaine self-administration is facilitated in rats pre-exposed to MDMA (Fletcher et al., 2001). Concurring with these results, we have demonstrated that exposure to MDMA or cocaine binges during adolescence induces long-lasting changes that increase the reinforcing effects of MDMA (Daza-Losada et al., 2009b). We observed that only mice previously exposed to MDMA developed CPP after being conditioned with a sub-threshold dose of MDMA. On the other hand, although all the groups developed CPP after conditioning with 10 mg/kg of MDMA, the extinguished preference was reinstated only in animals exposed to MDMA or cocaine during adolescence, in which it also took longer for the preference to be extinguished. Extinction provides a measurement of the motivational properties of drugs, which are evident in the persistence of drug-seeking behaviour in the absence of the drug (Aguilar et al., 2009). This is a powerful means of assessing the incentive motivational properties of drug-paired stimuli or non-contingent drug administration in the reinstating response (Pulvirenti, 2003). However, when the two drugs were administered together, cocaine blocked the increases that MDMA induced in sensitivity to the MDMA-induced CPP and in vulnerability to reinstatement of the preference. Once again, as the two drugs were administered simultaneously, the competition for the same molecular target could have affected their action, leading to a weaker effect.

Most authors believe that increases in drug-induced CPP or self-administration observed in animals exposed to MDMA are due to the actions that MDMA exerts on the serotonergic system (Horan et al. 2000; Fletcher et al. 2001). However, in many cases, it has been reported that the MDMA regimen employed did not induce dopaminergic or serotonergic

neurotoxicity, which was indeed the case in the studies mentioned above. None of the drugs, whether administered alone or together, induced significant changes in the concentration of these monoamines in the striatum, cortex or hippocampus 3 weeks later, at which time CPP was initiated (Daza-Losada et al. 2008b). Moreover, the chosen CPP schedule did not affect the concentration of monoamines (Daza-Losada et al. 2007).

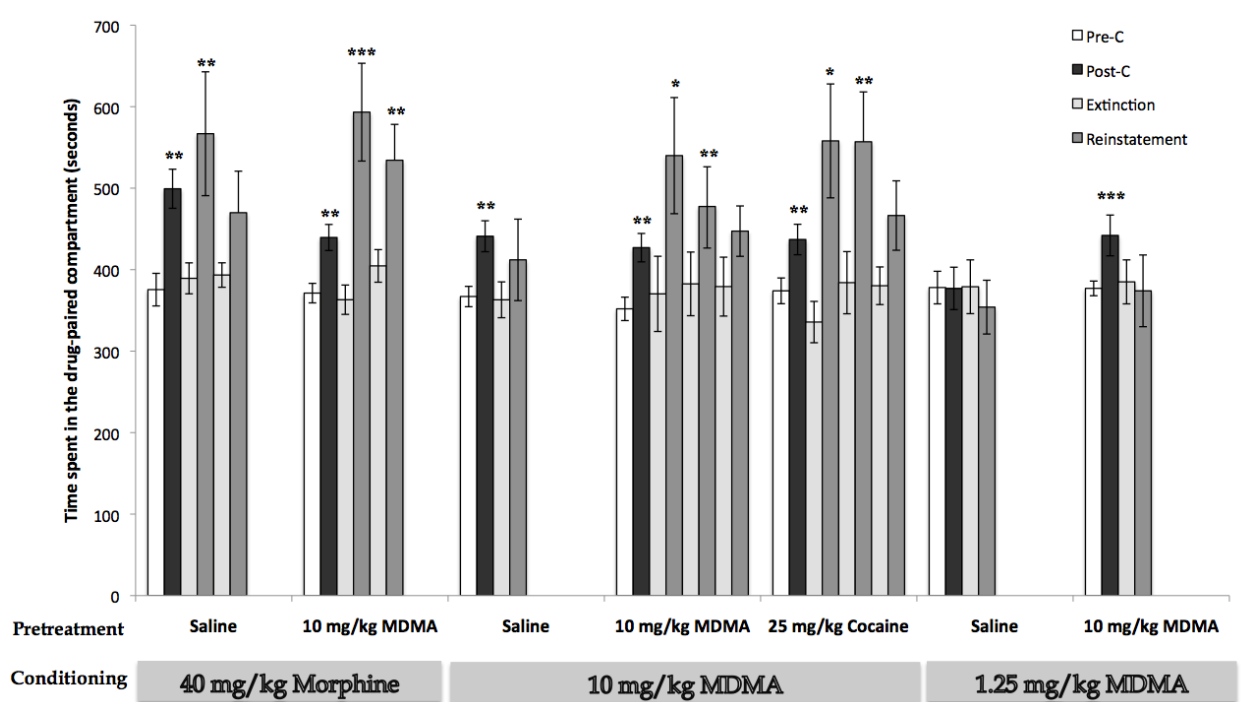


Fig. 2. Effects of MDMA or cocaine administration during adolescence on the acquisition and reinstatement of morphine or MDMA-induced CPP in adult mice. Bars represent mean (\pm SEM) time spent in the drug-paired compartment before conditioning session (\square), after conditioning session (\blacksquare), in the last extinction session (light grey), and in the reinstatement test (dark grey). During adolescence, mice were treated with six injections of physiological saline, 10 mg/kg of MDMA, or 25 mg/kg of cocaine. Three weeks later mice were conditioned with 40 mg/kg of morphine, or 10 mg/kg or 1.25 mg/kg of MDMA. After conditioning and extinction procedures, all animals received a priming injection of 50% of the drug dose administered during conditioning. In the subsequent reinstatement test, the priming doses employed were 25 and 12.5% that used during conditioning. MDMA exposure during adolescence increased the vulnerability to reinstatement of the extinguished preference induced by morphine and MDMA. This effect was also induced by administration of cocaine during adolescence. Pre-treatment with MDMA also increased its rewarding effects. * $p < 0,05$, ** $p < 0.01$, *** $p < 0.001$ significant difference in time spent in Post-C or Reinstatement tests vs. Pre-C session. Modified from Daza-Losada et al 2008b, 2009b).

6.2.2 MDMA and ethanol binges

Another drug often taken by adolescents in combination with ecstasy is alcohol (Riley et al., 2001; Barrett et al., 2006). Physiological and behavioural studies in humans and rodents have demonstrated an interaction between these two drugs (Mohamed et al., 2009). In humans, ethanol enhances and prolongs the euphoria and feelings of well-being induced by MDMA

(Hernández-López et al., 2002), but moderates some of its physiological effects, such as fluid retention and hyperthermia (Dumont et al., 2010). In addition, animal models have demonstrated that the hyperpyretic effect of MDMA is modulated by Ethanol according to the moment of ethanol administration and ambient temperature (Cassel et al., 2004, 2005 and 2007).

Research has only recently begun to use animal models to evaluate ethanol-MDMA interactions. Ethanol was shown to increase MDMA concentrations not only in blood but also, and to a greater extent, in the striatum and cortex than in the hippocampus (Hamida et al. 2009). On the other hand, levels of alcohol dehydrogenase 2, which metabolizes ethanol to acetaldehyde, were found to be 35% lower in MDMA-treated rats than in controls (Upreti et al. 2009). EthOH significantly potentiates the MDMA-induced outflow of serotonin and DA in rat striatal slices (Riegert et al., 2008). EthOH also affects the neurotoxicity induced by MDMA, although discrepant results have been reported. In rats, EtOH treatment before MDMA administration enhances long-term neurotoxicity, while in mice, EtOH protects DA neurons from the toxic effects of MDMA when evaluated 72 h after the first injection (Johnson et al., 2004). At the behavioural level, EtOH administration potentiates MDMA-induced hyperlocomotion in rats (Cassel, et al. 2004; Riegert, et al. 2008), and repeated co-administration of the two drugs results in a pronounced sensitization of hyperactivity (Hamida et al., 2007, 2008). Recently, Jones and co-workers (2010) have reported CPP in rats that received MDMA plus ethOH but not in those administered just with one of these drugs. These results suggest that acute co-administration of EtOH plus MDMA potentiates the reinforcing effects of each drug alone. Moreover, administration of EtOH would appear to increase the risk of compulsive use of MDMA.

A small number of studies have evaluated chronic exposure to both ethOH and MDMA, and none have explored this interaction in adolescent animals. Employing a model of binge drinking in which animals are treated during adolescence with intermittent doses of ethOH (a total of 16 doses administered intraperitoneally; two per day for two days, followed by a two-day interval without drugs), we aimed to imitate the pattern of weekend binge drinking that is currently so common among adolescents.

Mice were injected twice per day on postnatal day 29, 30, 33, 34, 37, 38, 41, and 42 and with MDMA twice daily on postnatal day 33, 34, 41, and 42. The behavioural and neurochemical test took place three weeks after the last drug administration. Pascual and co-workers (2007) demonstrated that this pattern of ethOH administration during adolescence enhances neural cell death in several brain regions (neocortex, hippocampus, and cerebellum) and induces long-lasting neurobehavioural impairments in conditional discrimination learning as well as motor learning and discrimination between novel and familiar objects. We too have observed that exposure to ethOH during adolescence increases the anxiogenic response induced by MDMA in the elevated plus maze, with adult treated-mice spending less time in the open arms of the maze than non treated littermates. In addition, although ethOH undermines the hyperthermic response induced by MDMA, animals exposed to ethOH plus MDMA exhibit lower concentrations of DA in the striatum than those treated with MDMA only (Rodríguez-Arias et al., 2011). In the study in question, though ethanol efficiently decreased the hyperthermic response induced by MDMA, it did not protect mice treated with 20 mg/kg of MDMA and actually increased the toxic effect in those treated with 10 mg/kg of MDMA, in which a hypothermic response was observed. This effect could be the

result of binge pattern ethOH administration enhancing MDMA-induced long-term neurotoxicity through a mechanism that is unrelated to changes in acute hyperthermia and which is thought to involve hydroxyl radical formation (Izco et al., 2007). All the groups that presented reduced levels of striatal DA exhibited increased levels of anxiety. We have previously observed that adolescent mice treated with a schedule of MDMA that provoked a similar decrease in DA concentration without alterations in DOPAC levels behave normally in the elevated plus maze (Daza-Losada et al. 2008b). However, in our study, the decrease in DA was accompanied by a considerable decrease in DOPAC levels, which may have been responsible for the behavioural differences observed. Dopamine plays an important role in anxiety by modulating a cortical brake that the medial prefrontal cortex exerts on the anxiogenic output of the amygdala. It also has a considerable influence on the trafficking of impulses between the basolateral and central nuclei of the amygdala. Intra-amygdaloid infusion of D1 agonists and antagonists elicits anxiogenic and anxiolytic effects, respectively, suggesting an anxiogenic role for D1 receptors in the amygdala. Analyses of the effects of D2 agonists and antagonists suggest that, depending on the model of anxiety in question, either anxiogenic or anxiolytic effects are elicited (de la Mora et al., 2010).

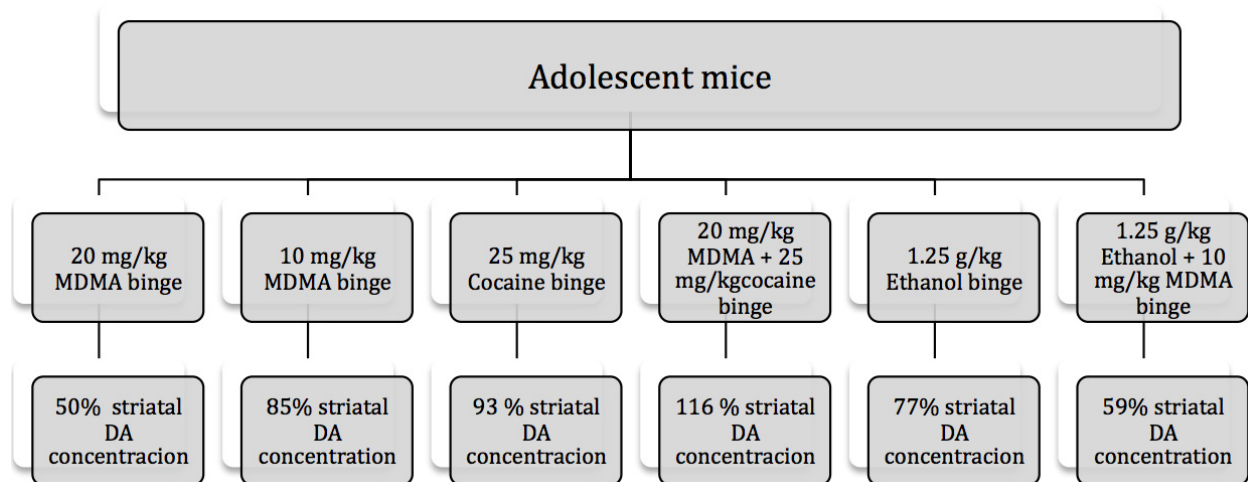


Fig. 3. Effects of MDMA, cocaine or ethanol binge administration during adolescence on the striatal DA concentration three weeks after the last drug administration. Co-administration of cocaine counteracted the neurotoxic effect of binge administration of 20 mg/kg of MDMA. However, intermittent ethanol administration increased the dopaminergic decrease induced by a non-neurotoxic dose (10 mg/kg) of MDMA. *** $p < 0.001$ differences with respect to the saline group. Modified from Daza-Losada et al 2008a, and Rodriguez-Arias et al., 2011.

In addition to inducing long-term consequences for the rewarding effects of drugs, any manipulation or intervention during adolescence can produce other changes, such as the reactivity of the HPA axis to different stressful situations. In a series of recent reports (Ribeiro do Couto et al., 2011a, 2011b), we observed that exposure during adolescence to intermittent injections of ethOH or MDMA modify the response of mice to MDMA administration in adulthood, in addition to previous reports that pointed out long-term behavioural (an increase in anxiety) and neurochemical (a rise in MDMA-induced neurotoxicity) effects (Rodriguez-Arias et al., 2011). Pre-exposure to ethOH, MDMA or both increased the rewarding effects of an ineffective dose of MDMA (1.25 mg/kg). Although

these pre-treatments did not affect acquisition of the CPP induced by higher doses, the preference was more persistent in mice pre-exposed to MDMA, ethOH or to both drugs. In addition, reinstatement of the extinguished preference was achieved with lower priming doses of MDMA in the groups pre-exposed to ethOH or MDMA (Ribeiro do Couto et al., 2011a). These effects appear to be due to the changes in the rewarding effects of MDMA rather than unspecific effects such as changes in basal motor activity or stress levels. After conditioning adults mice with an effective (but non neurotoxic) dose of MDMA (10 mg/kg), we once again observed that MDMA or ethanol exposure during adolescence increased the time required to extinguish the preference induced by MDMA and that these effects were related with an increase in either brain monoamine or corticosterone levels in response to MDMA (Ribeiro do Couto et al., 2011b). Mice treated with ethanol after the priming injection presented a significant increase in striatal DA. It is possible that this stronger neurochemical response to the priming dose of MDMA increased the efficacy of conditioning, reflected in a greater resistance to extinction. Similarly, the administration of 10 mg/kg of MDMA led to higher corticosterone values in mice exposed to MDMA during adolescence, while the response to low-mild stressors or to 5 mg/kg of MDMA did not differ, which could produce a stronger learning during conditioning.

In these series of studies, the combination of intermittent administration of ethOH+MDMA did not produce synergistic effects at either behavioural or neurochemical levels. In fact, the combination of the two drugs would seem to counteract the behavioural and hormonal effects of MDMA observed when each is administered alone. These results are in line with the previously discussed observation that adolescent exposure to MDMA exerts more powerful and longer-lasting effects on an MDMA-induced CPP than exposure to cocaine+MDMA (Daza-Losada et al., 2009). In this case, it is possible that ethanol interferes with the metabolism of MDMA and with its penetration of, and/or elimination, from the brain, and that this is responsible for the lack of effects observed after co-administration. Evidence that ethanol increases brain and blood concentrations of MDMA (Johnson et al., 2004) implies an enhanced MDMA-based neurotoxicity and an increased liability to abuse (Hamida et al., 2009). Since no neurotoxic effects were observed after any of the drug pre-treatments measured in the first reinstatement test, our results could be explained by the fact that ethanol increases the concentration of MDMA in the brain. Indeed, we found that the rewarding effects of MDMA produced an inverted U-curve in function of dose, with high doses proving to be devoid of motivational effects (Daza-Losada et al., 2007).

6.3 Cross-reinstatement and sensitization studies

This last section is dedicated to other kinds of drug interaction, cross-reinstatement and sensitization phenomena. Cross-reinstatement can be defined as the reinstatement of extinguished drug-seeking by drugs other than the previously self-administered or conditioning drug. This phenomenon has been widely demonstrated in self-administration and CPP studies. Cross-reinstatement with drugs from different classes to that of the self-administered drug has been demonstrated using the self-administration model. Cannabinoid agonists, DA agonists and re-uptake inhibitors and morphine, among others, produce reinstatement of cocaine-seeking after self-administration of cocaine has ended (reviewed by Shalev et al., 2002). Similarly, amphetamine and cocaine produce reinstatement of heroin self-administration (De Vries et al., 1998). Some studies have also

demonstrated cross-reinstatement using the CPP paradigm. An extinguished cocaine-induced CPP can be reinstated by a priming injection of related psychostimulants (Itzhak & Martin, 2002), and of other drugs of abuse of different pharmacological classes (Romieu et al., 2004). In the same way, we observed that a cocaine or amphetamine priming following extinction reinstated morphine-induced CPP (Ribeiro Do Couto et al., 2005). In a series of recent studies, we have also observed cross-reinstatement between cannabinoids and MDMA in adolescent animals. Extinguished MDMA-induced CPP was reinstated after a priming injection of the CB1 cannabinoid agonist WIN 55212-2, but this phenomenon only occurred in animals exposed to the cannabinoid agonist during adolescence (Rodríguez-Arias et al., 2010). However, in mice conditioned with WIN 55212-2, a priming injection of MDMA was capable of reinstating the extinguished preference without pre-exposure (Manzanedo et al., 2010). Most authors agree that the mesocorticolimbic DA system is involved in cross-reinstatement. For instance, Wang et al. (2000) suggested that opiates and psychostimulants can all activate the mesolimbic DA system to release DA, which is a mechanism underlying the relapse to drug-seeking behaviour induced by morphine, cocaine or amphetamine. It is possible that one drug cross-primed the other via this common pathway, which is involved in incentive motivation and appetitive goal-directed behaviour (Wang et al., 2000). Such evidence of cross-reinstatement between drugs of different pharmacological classes has also been found in adolescents and suggests that, in drug-abstinent individuals, exposure to an addictive drug can produce intense craving for the previously abused drug and thus lead to relapse to drug-taking and dependence.

The repeated, intermittent administration of a variety of potentially addictive drugs produces persistent increases in their incentive motivational properties (Manzanedo et al., 2004, 2005; Shippenberg & Heidbreder, 1995). Age-related differences in psychostimulant sensitization profiles have been described (Laviola et al., 1995, 1999), with adolescent rats proving to be less vulnerable to MDMA-induced sensitization, only developing this response to MDMA when administered with a high dose and within a narrow margin of time (Aberg et al., 2007). In a recent study, we have evaluated for the first time the effect of adolescent exposure to cannabinoids on the reinforcing effects of MDMA (Rodríguez-Arias et al., 2010). On postnatal day 27, animals received the first of five daily injections of the cannabinoid agonist WIN55212-2, and three days later the place conditioning procedure for MDMA was initiated. In mice pre-exposed to cannabinoids, sub-threshold doses of MDMA induced CPP and reinstatement of an extinguished preference. In the same way, delta-9-tetrahydrocannabinol administration increased hedonic reactions to sucrose and the rise of dialysate DA in the shell of the NAc (de Luca et al., in press). These results endorse the gateway hypothesis, which is sustained by numerous epidemiological studies and suggests that prior exposure to cannabinoids encourages use of other illicit drugs such as psychostimulants (Lynskey et al., 2003). Few studies have tested this hypothesis in animal models, and those that have done so do not provide firm support for it. However, the adolescent brain is particularly sensitive to external and internal variables such as drug exposure, since this phase of development is characterized by active neural changes in, for example, synapse formation and elimination, in brain areas essential for behavioural and cognitive functions (Charmandari et al., 2003; Rice & Barone, 2000). Consequently, exposure to cannabis during the adolescent period may increase vulnerability to subsequent drug abuse disorders.

Authors	Treatment employed	Specie	Age	Behaviour studied/ model employed	Drugs of abuse	Results
Diller et al 2007	acute treatment	rats	adult	MDMA- or cocaine-induced CPP	MDMA and cocaine	Both drugs induced CPP when administered alone. Co-administration produced an antagonism, except at high doses
Daza-Losada et al., 2009a	acute treatment	mice	adolescent	Anxiety (EPM) and striatal monoamine levels	MDMA and cocaine	Anxiolytic response in the elevated plus maze and increased DA turnover in the striatum only when the two drugs were administered together
Braida & Sala, 2002	acute treatment	rats	adult	Self-administration of MDMA (ICV)	MDMA and cannabinoid agonist	Cannabinoid agonists potentiated the rewarding effects of MDMA
Manzanedo et al., 2010	acute treatment	mice	adolescent	MDMA- induced CPP	MDMA and cannabinoid agonist	Low dose of the CB1 agonist increased the rewarding effects of an ineffective dose of MDMA, but higher doses of the cannabinoid agonist weakened the preference induced by effective doses of MDMA
Robledo et al (2007)	acute treatment	mice	adult	THC-induced CPP	Δ 9-THC and MDMA	A sub-threshold dose of THC produced CPP in mice when combined with a non-rewarding dose of MDMA, but decreased the CPP induced by an effective dose of MDMA
Daza-Losada et al., 2008a	MDMA and cocaine binge during adolescence	mice	adolescent	Striatal monoamine levels	MDMA and cocaine	MDMA-induced long-lasting decreases in the concentration of striatal DA at high doses, but cocaine inhibited this effect
Daza-Losada et al., 2008b	MDMA binge during adolescence	mice	adolescent	Morphine-induced CPP	MDMA and morphine	Sensitivity to reinstatement of an extinguished preference was increased in morphine-induced CPP
Estelles et al., 2006	Prenatal cocaine administration	mice	adult	Morphine-induced CPP	Cocaine and morphine	Prenatal treatment with cocaine decreased the rewarding actions of morphine in adult offspring
Achat-Mendes et al., 2003	MDMA binge during adolescence	mice	adolescent	Cocaine-induced CPP	Cocaine and MDMA	A priming injection of cocaine after extinction reinstated a significantly higher CPP in mice previously exposed to MDMA during adolescence
Daza-Losada et al., 2009b	MDMA and cocaine binge during adolescence	mice	adolescent	MDMA- induced CPP	Cocaine and MDMA	Only mice previously exposed to MDMA developed CPP after conditioning with a sub-threshold dose of MDMA. The extinguished preference was reinstated only in animals exposed to MDMA or cocaine during adolescence
Jones et al (2010)	acute treatment	rats	adult	MDMA- and EtOH-induced CPP	MDMA and EtOH	CPP was detected in rats that had received MDMA plus ethanol but not in those that had been administered just one of the drugs
Rodriguez-Arias et al., 2011	MDMA and EtOH binge during adolescence	mice	adolescent	Anxiety (EPM) and striatal monoamine levels	MDMA and EtOH	An increase was observed in the anxiogenic response induced by MDMA in adult mice treated with MDMA plus EtOH. EtOH increased the neurotoxic effect of MDMA
Ribeiro do Couto et al., 2011a, 2011b	MDMA and EtOH binge during adolescence	mice	adolescent	MDMA-induced CPP	MDMA and EtOH	Pre-exposure to EtOH, MDMA or both drugs increased the rewarding effects of an ineffective dose of MDMA. Reinstatement of the extinguished preference was achieved with lower priming doses of MDMA in the groups pre-exposed to ethanol or MDMA

Table 1. Synthesis of the most relevant interactions observed in the different models explained within the text.

7. Conclusion

In conclusion, the risks associated with multi-drug exposure during adolescence are still unclear. The high frequency of the combined used of several drugs in human adolescent users demands an in-depth evaluation of their interaction. It is obvious that the developing brain is highly vulnerable to the damaging effects of drugs; effects that can be irreversible. Studies performed to date demonstrate that the combined use of drugs produces a specific neurochemical and behavioural profile which differs to that observed when each drug is administered alone. These kinds of studies are more complicated to perform than those employing only one drug and involve many more variables that need to be controlled. Nevertheless, despite their complexity and the limitations inherent in their design, each of these studies constitutes a piece of a giant jigsaw puzzle which, as it is gradually put together, provides an increasingly clearer image of the reality of drug use.

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