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REVIEW ARTICLE

LONG TERM CONSEQUENCES OF IN UTERO ENDOCRINE DISRUPTORS EXPOSURE ON MALE OFFSPRING DEVELOPMENT

(Consecuencias a largo plazo de la exposición in utero a interruptores endócrinos sobre el desarrollo de la cría macho)

Maria Eugenia Pallarés and Marta C. Antonelli

Instituto de Biología Celular y Neurociencias "Prof. Eduardo De Robertis", Facultad de Medicina, Universidad de Buenos Aires, Argentina.

ABSTRACT

Early life events have long lasting impacts on tissue structure and function. It is accepted that there is an association between environmental challenge during pregnancy and later pathophysiology, a concept that has been named 'developmental programming' The environmental adversity acts on specific tissues of the foetus during sensitive periods in its development to change developmental trajectories and thus their organisation and function. During the prenatal period, gonadal steroid hormones (i.e. oestrogens and androgens) *organise* the developing brain by changing the architecture of several neural substrates which later in puberty are *activated* by the gonadal steroids surge in a directed manner. Endocrine disruptors may distort or shift the organism´s normal patterns of response to environmental or internal conditions and if present during the gestational period, severe morphological and functional impairments have been observed in the offpring. In this mini-review we will summarize the literature available on endocrine disruptors (ED) exposure during pregnancy and the influence on the outcome of the male offspring. Additionally, the effects of the non-steroidal ED flutamide will be discussed in view of the simmilarities detected with the prenatal stress effects observed on male offspring.

Keywords: *developmental programming; gonadal steroid hormones; male rat offspring; dopaminergic system; prenatal stress; flutamide.*

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1) SEXUAL DIFERENTIATION OF THE MALE REPRODUCTIVE TRACT

The primordial germ cells are the source of the spermatogonia cell line in males and oogonia in females. In males, the Y chromosome presents a gene called the testis determining factor (TDF) which initiates testicular differentation. The moment when the testis is first formed and the fetus distinguished as being a male is termed *sexual differentiation* (Brennan and Capel, 2004, Polanco and Koopman, 2007). The testes produce *mullerian duct inhibiting hormone* (MIH) which prevents the development and differentiation of the female internal reproductive organs and the testicular Leydig cells begin to produce *testosterone* which stimulates the development and differentiation of the Wolffian duct. The Wolffian duct gives rise to the male structures such as the ductus deferens, seminal vesicles and epididymis.

It is important to point out that the process by which the sexually indifferent fetus with a testis attains differentiated testes that secrete hormones and is transformed into a phenotypic male with internal and external male genitalia is called *masculinization.* The period during which the reproductive tract differentiate to the internal and external genitalia is called the *masculinization programming window* which in rats, roughly extends from embryonic day 17,5 to 19,5 (Scott et al., 2009).

Cholesterol is the precursor for all sex steroids and the influence of gonadal steroids on sexual differentiation becomes apparent after all steroid hormones and their receptors are functional. Testosterone, estrogen and their metabolites play important roles sexual differentiation, (Gorski, 2000, Karaismailoglu and Erdem, 2013).

Correspondence to: Dr. Marta C. Antonelli: Instituto de Biología Celular y Neurociencias "Prof. Eduardo De Robertis"; Facultad de Medicina, Universidad de Buenos Aires, Argentina. Dirección: Paraguay 2155, 3°Piso. (C1121ABG). Ciudad Autónoma de Buenos Aires, Argentina; Tel.: +54 11 5950-950056, Anexo 2240; E-mail: mca@fmed.uba.ar

Insufficient testosterone production or action during the masculinisation programming window in the foetal rat can result in disorders of masculinisation including malformation of the penis, cryptorchidism and reduced anogenital distance.

2) MASCULINIZATION OF THE BRAIN

It is now accepted that the reproductive system depends on the brain. Sexual dimorphism refers to the phenotypic differences between males and females of the same species and is observed not only in the reproductive system but also in the central nervous system and cognitive functions as well. As much as the genitalia, the regions of the brain directly involved with reproduction undergoes hormone-dependent sexual differentiation. This masculinization of the brain occurs perinatally in rodents (Arnold and Gorski, 1984, McCarthy and Konkle, 2005). Circulating testosterone can cross the blood–brain barrier and enter the cell, where it binds to its intracellular receptor. Testosterone can be converted to dihydrotestosterone (DHT) by 5-alpha reductase or to 17B-estradiol by aromatase enzymes. The direction of adult hormonal responsiveness will dictate sex-specific behaviour and physiology (Zhang et al., 2010). Although the main mechanism for masculinization of the brain is via the neural aromatization of testosterone to estrogen, DHT and other androgens also show effects through androgen receptors. In spite of the general belief that testosterone is the male hormone while estrogen and progesterone are the female sex hormones, in reality each sex has a particular balance of several hormones and the male fetal brain seems to be shaped according to a reciprocal interaction between estrogen receptors and androgen receptors. (Gorski, 2000, Karaismailoglu and Erdem, 2013).

The effect of gonadal hormones on brain maturation takes place at two different periods of life known as the classical organisational/activational hypothesis of gonadal steroid action (Phoenix et al., 1959, Alonso and Lopez-Coviella, 1998). During the prenatal period, gonadal steroid hormones) organise the developing brain by changing the architecture of several neural substrates which later in puberty are activated by the gonadal steroids surge in a directed manner. According to this classical view, brain architecture is modified in a permanent way by exposure of the male brain to testicular hormones during a brief perinatal period. More recently, this hypothesis has been challenged and the revised view of the period of organization/structural differentiation is extended from the postnatal period through puberty and adolescence in a prolonged postnatal sensitivity to the organizational effects of testicular hormones (Juraska et al., 2013).

3) ORGANIZATIONAL EFFECT ON THE DOPAMINERGIC SYSTEM

An efficient establishment of synaptic circuits during maturation is essential for the development of normal brain function. The majority of excitatory synapses are formed on dendritic spines and changes in spine density and morphology account for functional differences at the synaptic level (Segal, 2010). The cerebral cortex and the hippocampal formation are essential components of the neural pathways that mediate stress responses and are essential for learning and memory formation (Madeira and Lieberman, 1995). The mesocorticolimbic dopaminergic (DA) system, that comprises neurons from the ventral tegmental area (VTA) projecting mainly to the hippocampus and the prefrontal cortex (Kuhar et al., 1999, Chinta and Andersen, 2005, Baier et al., 2012), regulates diverse behavioural and cognitive functions that are crucial for the integration of individual perception and its adaptation to the environment (Missale et al., 1998).

Androgen organisational influence over mesostriatal and mesolimbic DA system was demonstrated by Creutz and Kritzer (2004). Moreover, Yang and Shieh (2007) suggested that gonadal hormones play a regulatory role in the stimulation of cocaine and amphetamine-regulated transcript peptide in mesolimbic and nigrostriatal DA system and Johnson et al (2010) demonstrated that testosterone play a suppressive role in midbrain DA pathways. The organisational role of androgens in hippocampus was explored by Zhang and collaborators (2010) who reported that neonatal androgenic surges disruption increased depression-like behaviours in prepubertal male rats as well as reduced the number of MAP2 (microtubule-associated protein type 2), immunopositive neurons in the dentate gyrus and the density of dendritic spines of the pyramidal neurons of the CA1 hippocampal areas.

4) ENDOCRINE DISRUPTORS IN MALE REPRODUCTIVE DEVELOPMENT

According to Weiss (2012) endocrine disruptors (ED) refers to "chemicals agents that interfere with the biological actions of hormones by blocking, mimicking, displacing, or acting through a variety of other mechanisms to subvert their natural roles" and may be divided into natural compounds mostly obtained from our diet and man-made chemicals used in the environment (such as herbicides, pesticides, plasticizers , industrial by-products, etc) (Hampl et al., 2014) or widely used therapeutic drugs (e.g., steroid hormones, statins, glitazones, fungicides, etc) (Scott et al., 2009). Unlike traditional toxicants that express their effect in the form of tissue pathology, clinical disorders or death, endocrine disruptors may distort or shift the organism´s normal patterns of response to environmental or internal conditions (Weiss, 2012). This shift from the normal pattern of internal conditions is particularly critical when the EDs exposure occurs during the perinatal period. Epidemiological and animal studies suggest that prenatal exposure to EDs such as phtalates and bisphenol A have adverse effects on birth weight, promote development of childhood obesity and adversely affect male reproductive tract development and reproductive disorders (DiVall, 2013). In relation to the male reproductive disorders, there is growing evidence that prenatal exposure to phtalates (Swan et al.,

2005, Zhang et al., 2010) and maternal occupational exposure to BPA (Miao et al., 2011) are associated with shorter anogenital distance in boys. Moreover, prenatal BPA exposure downregulates expression of genes associated with Sertoli cell function and affects the reproductive function of male mice offspring (Tainaka et al., 2012). Exposure of pregnant rhesus monkeys to relatively low levels of BPA during the final 2 months of gestation, induced abnormalities in fetal ventral mesencephalon and hippocampus. Specifically, light microscopy revealed a decrease in tyrosine hydroxylase-expressing neurons in the midbrain of BPA-exposed fetuses and electron microscopy identified a reduction in spine synapses in the CA1 region of hippocampus (Elsworth et al., 2013). For a comprehensive review on the differences in the susceptibility to disruption by exogenous compounds on the steroidogenesis between man and rodent in the fetal testis, please refer to Scott et al.(2009).

The steroidogenic cascade might be impacted negatively on testosterone production by therapeutic and environmental compounds at several points, but impaired testosterone production is not the only reason for failure or incomplete masculinization. It can also occur due to mutations of the androgen receptor (Hughes, 2001); 5a-reductase type 2 deficiency (Imperato-McGinley and Zhu, 2002) or to antiandrogenic drugs (McLeod, 1993). Antiandrogenic drugs, or androgen-receptor antagonists, represent a group of compounds that have been employed in the treatment of metastatic prostate cancer. Their method of action is basically by inhibiting androgen uptake and/or inhibition of nuclear binding of the androgens in the target tissues and they are classified as steroidal or nonsteroidal compounds. Cyproterone and megestrol are synthetic steroidal antiandrogenic drugs that, not only compete for androgen receptors, but also reduce plasma testosterone. Nonsteroidal antiandrogenic agents such as flutamide and nilutamide block cellular binding of androgens only, and there is no reduction of testosterone levels (McLeod, 1993). In particular, flutamide is a powerful and specific antiandrogen that crosses the placental barrier (Neri et al., 1972) and blocks AR by inhibiting its translocation to the nucleus from the cytoplasm of the target cells. Several groups have studied the effect of the administration of flutamide during the last week of gestation on the male offspring. Casto and collaborators (2003), observed that adult plasma levels of testosterone were not different in flutamide-exposed males and controls, but testicular and epididymal weight, anogenital distance, and penile length were reduced along with reductions in reproductive behaviors. Moreover, Imperato-McGinley et al. (1992) found that flutamide-treated (18 mg/kg.day) animals, Wolffian ductal differentiation occurred, but seminal vesicle weight was decreased, whereas at similar doses, (Goto et al., 2004) found decreased anogenital distance of the male offspring as well as cryptorchidism and absence of the prostate gland and seminal vesicles and changes in sexual behaviour. Similarly, (Okur et al., 2006) concludes that blocking of prenatal androgen with flutamide interferes with testicular development by inhibiting testicular descent, and also effects testicular morphology and function in both the descended and undescended testes of rats.

In our hands, male offpring of pregnant rats injected with flutamide (10 mg/Kg/day) from days 15-21 of gestation, showed reduced anogenital distance, delay in the completion of testis descent, hypospadias, cryptorchidism and atrophied seminal vesicles. Brain morphological studies revealed that prenatal flutamide decreased the number of MAP2 (present almost exclusively in dendrites) immunoreactive neuronal processes in all evaluated brain areas, both in prepubertal and adult offspring, suggesting that prenatal androgen disruption induces long term reductions of the dendritic arborisation of several brain structures, affecting the normal connectivity between areas. Moreover, the number of tyrosine hydroxylase immunopositive neurons in the VTA of prepubertal offspring was reduced in flutamide rats but reach normal values at adulthood (Pallares et al., 2014).

5) PRENATAL STRESS

During the last years, increasing evidences from rodent models demonstrate that exposure to different stressful events during the last week of gestation strongly impacts on structural and functional foetal central nervous system development, leading to impaired adaptation to stressful conditions, enhanced propensity to self-administer drugs, vulnerability to anxiety and learning deficits (Weinstock, 2001, Huizink et al., 2004, Darnaudery and Maccari, 2008, Weinstock, 2008). In addition, the offspring display anomalies in neuronal development and brain morphology which persist into adulthood (Fride and Weinstock, 1989). Our laboratory has a long standing interest in the effects of prenatal stress on the brain development, especially on the mesocorticolimbic DA pathway (Baier et al., 2012) triggered by the hypothesis that stressful situations suffered prenatally are related to the propensity to develop psychiatric abnormalities in the adult life.

We investigated the effects of prenatal stress on expression of DA and glutamatergic (Glu) receptors using quantitative autoradiography in offsprings of dams subjected to restrain stress during the last week of gestation. DA receptors increased in limbic areas of the adult brain whereas Glu receptors increased both in limbic and motor areas (Berger et al., 2002). Adoption at birth was used to change the postnatal environment and the complex pattern of receptor changes obtained reflects the high vulnerability of DA and Glu systems to variations both in prenatal and in postnatal environment (Barros et al., 2004). Behavioral studies have also been carried out and adult offspring of rats stressed during pregnancy exhibited higher levels of anxiety than control rats. The anxiety levels show direct correlation with benzodiazepine receptors exhibiting a decrease in the number of benzodiazepine receptors binding sites in amygdala and hippocampus (Barros et al., 2006b). We also performed morphological studies to evaluate astrocytes and dendritic arborization in frontal cortex, striatum and hippocampus of the prenatally stressed adult rat brain. These results demonstrate that prenatal stress induces a

long-lasting astroglial reaction and a reduced dendritic arborization with synaptic loss in the brain of adult offspring (Barros et al., 2006a). Specific dopaminergic transcriptions factors (Nurr1 and PiTX3) were found to be altered in PS offspring along with the expression of TH. (Katunar et al., 2009, Katunar et al., 2010). Amphetamine or nicotine stimulation produces an increase in DA levels in NAc-S of adult PS male rats (Silvagni et al., 2008) and a decreased DA release after amphetamine stimulation in PFC of adult offspring (Carboni et al., 2010), suggesting that this cortical dopaminergic deficit might be triggering a NAc hyperfunction and an overall dopaminergic imbalance in the prenatally stressed brain.

We have demonstrated that several impairments induced by prenatal stress on the DA metabolism were differentially affected if assayed before or after puberty. This observation confirms the suggestion from previous investigations that perinatal events might render the DA circuitry more vulnerable to puberty variation of the hormonal circulating levels (Diaz et al., 1997). However, the reduction in dendritic arborisations induced by prenatal stress in PFC and HPC, that were reported to occur at adult stages (Barros et al., 2006b), were also found prepubertally (Pallares et al., 2013a), suggesting that some plastic morphological processes might be programmed prenatally but are relatively insensitive to the increase of sexual hormones during puberty.

However, the occurrence of some factors during this perinatal phase can interfere with the physiological, morphological, behavioural, and neuroanatomical differences between males and females (Scott et al., 2009). For example, it was reported that prenatal stress supresses the surge of prenatal testosterone, affecting the male reproductive tract formation, inducing abnormal testosterone levels and feminising the male sexual behaviour (Shono and Suita, 2003, Barros et al., 2004, Gerardin et al., 2005). In our hands, we have shown that prenatal stress induced long-term imbalance of male sexual hormones concentrations in serum, advanced the spermatogenesis development and exerted an age-dependent misbalance on oestrogen alpha receptor expression on PFC and HPC brain areas (Pallares et al., 2013a, Pallares et al., 2013b). Moreover, it was observed that physiological and behavioural damage caused by prenatal stress were prevented by replacement with neonatal testosterone (Pereira et al., 2006), corroborating the importance of neonatal testosterone surge during the sexual differentiation process of the brain.

The striking simmilarities among the results obtained between the prenatal stress paradigm and prenatal flutamide exposure prompt us to suggest that prenatal administration of flutamide might impair sexual maturation as well as brain morphology development in the prepubertal and adult offspring in a similar manner to the exposure of stress during late gestation that was previously reported by our group. In this regards, we suggested that the mechanism of action of prenatal stress might be related to the impairment of the organisational role of androgens on brain development.

6) CONCLUDING REMARKS

The process by which the sexually indifferent foetus with a testis attains differentiated testes that secrete hormones and is transformed into a phenotypic male is called *masculinisation*. As much as the genitalia, the regions of the brain directly involved with reproduction undergoes hormone-dependent sexual differentiation, a process known as *masculinisation of the brain* which in rodents occurs perinatally.

The effect of gonadal hormones on brain maturation takes place at two different periods of life known as the classical *organisational/activational hypothesis of gonadal steroid action*. The direction of adult hormonal responsiveness will dictate sex-specific behaviour and physiology, and in particular, the mesocorticolimbic DA system regulates diverse behavioural and cognitive functions that are crucial for the integration of individual perception and its adaptation to the environment. It has been widely demonstrated that androgens have an organisational influence over mesostriatal and mesolimbic DA system as well as in the hippocampus.

ED may distort or shift the organism normal patterns of response to environmental or internal conditions, that if it temporally occurs during the prenatal period, adverse outcomes were observed such as: reduction on birth weight, childhood obesity, shorter anogenital distance in boys, and alterations in the reproductive function of male mice offspring. At the central nervous system level, abnormalities in foetal ventral mesencephalon and hippocampus such as a decrease in tyrosine hydroxylase-expressing neurons in the midbrain and a reduction in spine synapses in the CA1 region of hippocampus were reported. The exposure of pregnant dams to the nonsteroidal ED flutamide shows reductions in testicular and epididymal weight, anogenital distance, and penile length along with reductions in reproductive behaviours of the male offspring. Moreover, seminal vesicle weight and anogenital distance were decreased, as well as cryptorchidism and absence of the prostate gland and seminal vesicles. Testicular descent was inhibited along with affected testicular morphology and function in both the descended and undescended testes of rats. In our hands, male offspring of pregnant rats injected with flutamide showed reduced anogenital distance, delay in the completion of testis descent, hypospadias, cryptorchidism and atrophied seminal vesicles. Brain morphological studies revealed that prenatal flutamide induced reductions of the dendritic arborisation of several brain structures, and reductions in the number of tyrosine hydroxylase immunopositive neurons in the VTA of prepubertal offspring.

The striking similarity of these results with those obtained in the male offspring when the mother was stressed during the last week of gestation, prompted us to suggest that a possible mechanism by which PS exerts its effects on the offspring development might be similar to the antiandrogenic

mechanism exert by flutamide, therefore impairing the organisational role of androgens on brain development.

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REFERENCES:

Alonso R, Lopez-Coviella I (Gonadal steroids and neuronal function. Neurochem Res 23:675-688.1998).

Arnold AP, Gorski RA (Gonadal steroid induction of structural sex differences in the central nervous system. Annu Rev Neurosci 7:413-442.1984).

Baier CJ, Katunar MR, Adrover E, Pallares ME, Antonelli MC (Gestational Restraint Stress and the Developing Dopaminergic System: An Overview. Neurotox Res.2012).

Barros VG, Berger MA, Martijena ID, Sarchi MI, Perez AA, Molina VA, Tarazi FI, Antonelli MC (Early adoption modifies the effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. J Neurosci Res 76:488-496.2004).

Barros VG, Duhalde-Vega M, Caltana L, Brusco A, Antonelli MC (Astrocyte-neuron vulnerability to prenatal stress in the adult rat brain. J Neurosci Res 83:787-800.2006a).

Barros VG, Rodriguez P, Martijena ID, Perez A, Molina VA, Antonelli MC (Prenatal stress and early adoption effects on benzodiazepine receptors and anxiogenic behavior in the adult rat brain. Synapse 60:609-618.2006b).

Berger MA, Barros VG, Sarchi MI, Tarazi FI, Antonelli MC (Long-term effects of prenatal stress on dopamine and glutamate receptors in adult rat brain. Neurochem Res 27:1525-1533.2002).

Brennan J, Capel B (One tissue, two fates: molecular genetic events that underlie testis versus ovary development. Nat Rev Genet 5:509-521.2004).

Carboni E, Barros VG, Ibba M, Silvagni A, Mura C, Antonelli MC (Prenatal restraint stress: an in vivo microdialysis study on catecholamine release in the rat prefrontal cortex. Neuroscience 168:156-166.2010).

Casto JM, Ward OB, Bartke A (Play, copulation, anatomy, and testosterone in gonadally intact male rats prenatally exposed to flutamide. Physiol Behav 79:633-641.2003).

Creutz LM, Kritzer MF (Mesostriatal and mesolimbic projections of midbrain neurons immunoreactive for estrogen receptor beta or androgen receptors in rats. J Comp Neurol 476:348-362.2004).

Chinta SJ, Andersen JK (Dopaminergic neurons. Int J Biochem Cell Biol 37:942-946.2005).

Darnaudery M, Maccari S (Epigenetic programming of the stress response in male and female rats by prenatal restraint stress. Brain Res Rev 57:571-585.2008).

Diaz R, Fuxe K, Ogren SO (Prenatal corticosterone treatment induces long-term changes in spontaneous and apomorphine-mediated motor activity in male and female rats. Neuroscience 81:129-140.1997).

DiVall SA (The influence of endocrine disruptors on growth and development of children. Curr Opin Endocrinol Diabetes Obes 20:50-55.2013).

Elsworth JD, Jentsch JD, Vandevoort CA, Roth RH, Jr DE, Leranth C (Prenatal exposure to bisphenol A impacts midbrain dopamine neurons and hippocampal spine synapses in non-human primates. Neurotoxicology 35:113-120.2013).

Fride E, Weinstock M (Alterations in behavioral and striatal dopamine asymmetries induced by prenatal stress. Pharmacol Biochem Behav 32:425-430.1989).

Gerardin DC, Pereira OC, Kempinas WG, Florio JC, Moreira EG, Bernardi MM (Sexual behavior, neuroendocrine, and neurochemical aspects in male rats exposed prenatally to stress. Physiol Behav 84:97-104.2005).

Gorski R (2000) Sexual differentiation of the nervous system. In: Principles of Neural Science(Hill, M. G., ed), pp 1131-1148 New York.

Goto K, Koizumi K, Takaori H, Fujii Y, Furuyama Y, Saika O, Suzuki H, Saito K, Suzuki K (Effects of flutamide on sex maturation and behavior of offspring born to female rats treated during late pregnancy. J Toxicol Sci 29:517-534.2004).

Hampl R, Kubatova J, Starka L (Steroids and endocrine disruptors-History, recent state of art and open questions. J Steroid Biochem Mol Biol.2014).

Hughes IA (Minireview: sex differentiation. Endocrinology 142:3281-3287.2001).

Huizink AC, Mulder EJ, Buitelaar JK (Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? Psychol Bull 130:115-142.2004).

Imperato-McGinley J, Sanchez RS, Spencer JR, Yee B, Vaughan ED (Comparison of the effects of the 5 alpha-reductase inhibitor finasteride and the antiandrogen flutamide on prostate and genital differentiation: dose-response studies. Endocrinology 131:1149-1156.1992).

Imperato-McGinley J, Zhu YS (Androgens and male physiology the syndrome of 5alpha-reductase-2 deficiency. Mol Cell Endocrinol 198:51-59.2002).

Johnson ML, Day AE, Ho CC, Walker QD, Francis R, Kuhn CM (Androgen decreases dopamine neurone survival in rat midbrain. J Neuroendocrinol 22:238-247.2010).

Juraska JM, Sisk CL, DonCarlos LL (Sexual differentiation of the adolescent rodent brain: hormonal influences and developmental mechanisms. Horm Behav 64:203-210.2013).

Karaismailoglu S, Erdem A (The effects of prenatal sex steroid hormones on sexual differentiation of the brain. J Turk Ger Gynecol Assoc 14:163-167.2013).

Katunar M, Saez T, Brusco A, Antonelli M (Inmunocytochemical expression of dopamine-related transcription factors Pitx3 and Nurr1 in prenatally stressed adult rats. Journal of Neuroscience Research 87:1014-1022.2009).

Katunar M, Saez T, Brusco A, Antonelli M (Ontogenetic Expression of dopamine-Related Transcription Factors and Tyrosine Hydroxylase in Prenatally Stressed Rats. Neurotoxicity Research 18:69-81.2010).

Kuhar MJ, Couceyro PR, Lambert PD (1999) Catecholamines. In: Basic Neurochemistry: Molecular, Cellular, and Medical Aspects. (Siegel, G. J., Agranoff, B.W, Albers, R.W, Fisher, S.K, Uhler, M.D. Uhler eds., ed) Lippincott,Williams & Wilkins, Philadelphia.

Madeira MD, Lieberman AR (Sexual dimorphism in the mammalian limbic system. Prog Neurobiol 45:275-333.1995).

McCarthy MM, Konkle AT (When is a sex difference not a sex difference? Front Neuroendocrinol 26:85-102.2005).

McLeod DG (Antiandrogenic drugs. Cancer 71:1046-1049.1993).

Miao M, Yuan W, He Y, Zhou Z, Wang J, Gao E, Li G, Li DK (In utero exposure to bisphenol-A and anogenital distance of male offspring. Birth Defects Res A Clin Mol Teratol 91:867-872.2011).

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (Dopamine receptors: from structure to function. Physiol Rev 78:189-225.1998).

Neri R, Florance K, Koziol P, Van Cleave S (A biological profile of a nonsteroidal antiandrogen, SCH 13521 (4'-nitro-3'trifluoromethylisobutyranilide). Endocrinology 91:427-437.1972).

Okur H, Muhtaroglu S, Bozkurt A, Kontas O, Kucukaydin N, Kucukaydin M (Effects of prenatal flutamide on testicular development, androgen production and fertility in rats. Urol Int 76:130-133.2006).

Pallares ME, Adrover E, Baier CJ, Bourguignon NS, Monteleone MC, Brocco MA, Gonzalez-Calvar SI, Antonelli MC (Prenatal maternal restraint stress exposure alters the reproductive hormone profile and testis development of the rat male offspring. Stress 16:429-440.2013a).

Pallares ME, Adrover E, Imsen M, Gonzalez D, Fabre B, Mesch V, Baier CJ, Antonelli MC (Maternal administration of flutamide during late gestation affects the brain and reproductive organs development in the rat male offspring. Neuroscience 278C:122-135.2014).

Pallares ME, Baier CJ, Adrover E, Monteleone MC, Brocco MA, Antonelli MC (Age-dependent effects of prenatal stress on the corticolimbic dopaminergic system development in the rat male offspring. Neurochem Res 38:2323-2335.2013b).

Pereira OC, Bernardi MM, Gerardin DC (Could neonatal testosterone replacement prevent alterations induced by prenatal stress in male rats? Life Sci 78:2767-2771.2006).

Phoenix CH, Goy RW, Gerall AA, Young WC (Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65:369-382.1959).

Polanco JC, Koopman P (Sry and the hesitant beginnings of male development. Dev Biol 302:13-24.2007).

Scott HM, Mason JI, Sharpe RM (Steroidogenesis in the fetal testis and its susceptibility to disruption by exogenous compounds. Endocr Rev 30:883-925.2009).

Segal M (Dendritic spines, synaptic plasticity and neuronal survival: activity shapes dendritic spines to enhance neuronal viability. Eur J Neurosci 31:2178-2184.2010).

Shono T, Suita S (Disturbed pituitary-testicular axis inhibits testicular descent in the prenatal rat. BJU Int 92:641-643.2003).

Silvagni A, Barros V, Mura M, Antonelli M, Carboni E (Prenatal restrain stress differentially modifies basal and stimulated dopamine and noradrenaline release in the rat nucleus accumbens shell: an “in vivo” microdialysis study. Eur J of Neuroscience En prensa.2008).

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL (Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 113:1056-1061.2005).

Tainaka H, Takahashi H, Umezawa M, Tanaka H, Nishimune Y, Oshio S, Takeda K (Evaluation of the testicular toxicity of prenatal exposure to bisphenol A based on microarray analysis combined with MeSH annotation. J Toxicol Sci 37:539-548.2012).

Weinstock M (Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Prog Neurobiol 65:427-451.2001).

Weinstock M (The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev 32:1073-1086.2008).

Weiss B (The intersection of neurotoxicology and endocrine disruption. Neurotoxicology 33:1410-1419.2012).

Yang SC, Shieh KR (Gonadal hormones-mediated effects on the stimulation of dopamine turnover in mesolimbic and nigrostriatal systems by cocaine- and amphetamine-regulated transcript (CART) peptide in male rats. Neuropharmacology 53:801-809.2007).

Zhang JM, Tonelli L, Regenold WT, McCarthy MM (Effects of neonatal flutamide treatment on hippocampal neurogenesis and synaptogenesis correlate with depression-like behaviors in preadolescent male rats. Neuroscience 169:544-554.2010).

RESUMEN

Los eventos de vida tempranos producen un impacto de largo alcance sobre la función y la estructura de los tejidos. En la actualidad se acepta que existe una asociación entre el desafío ambiental durante la gestacion y la patofisiología posterior, concepto que se ha denominado “programación del desarrollo”. La adversidad ambiental actúa sobre tejidos específicos del feto durante períodos sensibles que cambian trayectorias del desarrollo y consecuentemente su organización y función. Durante el periodo prenatal, las hormonas esteroideas gonadales (estrógenos y andrógenos) organizan el cerebro en desarrollo cambiando la arquitectura de varios sustratos neurales que luego en la pubertad son activados por los esteroides gonadales en forma directa. Los interruptores endocrinos (IE) pueden distorsionar o correr los patrones normales de respuesta a las condiciones internas o ambientales. Se ha observado que si los mismos se se encuentran presentes durante el período gestacional se producen alteraciones severas en la función y la morfología de la cría. En este trabajo de revision, resumiremos la bibliografia existente sobre la exposición a IE durante la gestación asi como la influencia sobre el desarrollo de la cría macho. Por otra parte, discutiremos el efecto del IE no-esteroideo Flutamida en vista de las similaridades detectadas con los efectos del estrés prenatal observado en crías macho.

Palabras Claves: *Programación del desarrollo, hormonas esteroideas gonadales, sistema dopaminérgico, receptores androgénicos, estrés prenatal, flutamida, gestación, rata.*

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