

*To the memory of my friends and colleagues  
Prof. Luciano Martini (Italy)  
and Prof. Gunter Dörner (Germany)*

# Our half-century quest to understand the etiology and pathogenesis of developmental disturbances of neuroendocrine control of reproduction and endocrine stress response (mini-review)

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**Abstract.** The review article summarizes the main results of half a century of experimental research of the Department of Endocrinology of Reproduction and Adaptation in the field of congenital defects of the neuroendocrine system caused by pathogenic influences on the mother's body during critical periods of individual development. A neurochemical concept of androgen-dependent disorders of sexual differentiation of the brain is proposed, which relate to the regulation of ovarian cycles, sexual behavior, the function of the hypothalamic-pituitary-adrenal axis and its response to stress. The role of corticosteroids in the early programming of the hypothalamic-pituitary-adrenal axis of intrauterine fetus is shown. The neurohormonal mechanisms of the pathogenesis of prenatal stress syndrome are revealed and the ways of pharmacological prevention of its negative long-term consequences are outlined. Long-term effects of prenatal exposure to dibutyl phthalate, bisphenol A and ibuprofen as endocrine disruptors were studied. A new syndrome of hypersexuality and hyperandrogenism is described in male rats after maternal exposure to low doses of dibutyl phthalate during the critical period of sexual differentiation of the fetal brain. **Conclusions.** The research findings indicate the importance of further research in the field of so-called functional teratology. They are the pathogenetic basis for the prevention of a number of neuroendocrine and behavioral disorders.

**Keywords:** brain, sexual differentiation, neuroendocrine system, prenatal stress, sexual behavior, endocrine disruptors, rat.

For many years, the Department of Endocrinology of Reproduction and Adaptation (former

Laboratory of Neurohormonal Control of Reproduction), which I am heading since 1973 to present, conducts animal research in the fields of

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endocrine physiology, pathophysiology, pharmacology and oncology. Exploration of phenomena and mechanisms of the early and long-term neuroendocrine and behavioral consequences of various early-life influences on developing neuroendocrine system were kept as a mainstream of our research team activities [1-13]. Some of the results of these studies are presented in this review.

One of the mysterious phenomena was the formation of sexual differences in behavior and other physiological functions regulated by the neuroendocrine system. In the middle of the last century, it was found that epigenetic programming of the male type of these functions occurs in early life under the influence of testicular testosterone, while the female type is determined exclusively by the genome. This process occurs in the human fetal brain during the middle trimester of pregnancy, and in rodents in the pre- and early postnatal period, and is known as the sexual differentiation of the brain (SDB). The study of this problem made it possible to understand the pathogenesis of disorders of the ovulatory-menstrual cycles, infertility and sexual behavior deviations in some women born to mothers with hyperandrogenic conditions.

We started to work on neonatally androgenized female (NAF) rats trying to clarify changes in hormonal profile and leading neurochemical mechanisms underlying disturbances of SDB. For this purpose, testosterone propionate was administered to 2-5-day-old females. In adulthood, they demonstrated polycystic ovaries, anovulation, persistent estrous infertility, decreased levels of adenohipophyseal bioactive luteinizing hormone and hypothalamic gonadoliberin, as well as reduction of the uptake of 6,7-<sup>3</sup>H-estradiol-17 $\beta$  (10 Ki/mM) by the hypothalamus, adenohipophysis and uterus tissues. Ovarian and blood plasma progesterone levels reduced significantly. Neonatal injection of testosterone propionate induced homo- or bisexual behavior and significant defeminization of the female-type sexual behavior. In particular, the lordosis index in NAF who were ovariectomized and primed with estradiol and progesterone decreased ten times.

Regarding the hypothalamic-pituitary-adrenal axis (HPAA), we have shown that plasma corticosterone response to an acute restriction stress was completely absent in contrast to normal females. This phenomenon was found to be

associated with low levels of hypothalamic norepinephrine and impaired noradrenergic response to restriction stress. It should be emphasized that these experiments with the stereotaxic administration of norepinephrine were carried out on unanesthetized, freely moving animals in a cage, with periodic blood sampling from a catheterized heart for a period of one and a half hours.

Interestingly, there is coincidence in time between the organizing effect of sex hormones on the brain and the maturation of HPAA [14]. It was shown that long-term disorders of HPAA in NAF are associated with changes in the expression of corticoliberin mRNA and decline of corticoliberin content in the hypothalamus, as well as an increase in the content of glucocorticoid receptor in hypothalamic paraventricular nuclei [15].

The disorders of SDB were evidenced by attenuation of sexual differences of the spectrum of soluble cytosolic proteins in the discrete sex-dimorphic brain areas of NAF and normal males at postnatal days 5 and 10.

We focused on studying the preoptic area (POA) of the hypothalamus because it is associated with the regulation of male sexual behavior in rodent males. We have found that an early marker of SDB and an important mechanism in the pathogenesis of its disorder was steroid aromatase activity (SAA) in the POA. At postnatal day 10, conversion of [1,2,6,7-<sup>3</sup>H] testosterone to radiolabeled estradiol-17 $\beta$  in the presence of a NADPH-generating system was 3-5 times higher in the POA of normal males in comparison with normal females. In the NAF, sex difference in the POA SAA disappeared due to its elevation.

Pathogenetic relevance of SAA in programming the NAF brain on the male type has been proven by significant reduction of occurrence of anovulation and persistent estrus in adult rats as result of inhibition of hypothalamic SAA with androst-1,4,6-trien-3,17-dion or androst-4-en-3,6,17-trion before neonatal androgenization.

It was reported that neonatally administered testosterone induces an increase in the concentration of norepinephrine in the whole brain of newborn female rats. We hypothesized that this is due to catechol estrogens, which are formed locally from testosterone-derived estradiol and compete with norepinephrine for binding sites on catechol-*O*-methyltransferase, and in this way

slows down the metabolism of norepinephrine, causing its accumulation in the hypothalamus. In support of this hypothesis, it turned out that SAA inhibitors prevent an increase in the norepinephrine content in the hypothalamus of NAF, whereas 4-hydroxyestradiol-17 $\beta$ , unlike other studied catechol estrogens isomers, causes it to rise.

To clarify whether testosterone-induced increase in the content of norepinephrine in the hypothalamus is an associated phenomenon or is critically important for SDB, testosterone was administered to newborn females against the background of blockade of catecholamine synthesis by  $\alpha$ -methyl-*p*-tyrosine. This drug prevented anovulation and preserved the proestrus surge of LH. On the other hand, an increase in the level of norepinephrine in the hypothalamus by the administration of tropolone, catechol-*O*-methyltransferase inhibitor, without testosterone did not disturb SDB. Moreover, the addition of tropolone to testosterone augmented the severity of anovulatory syndrome. Noticeably, blockade of adrenergic receptors was not capable of interfering with testosterone to disrupt SDB. We concluded that norepinephrine is involved in androgen-dependent SDB together with estrogen / catechol estrogen, and both of them function as non-synaptic inducers of neurocyte differentiation. The discovery of non-synaptic effects of norepinephrine was first demonstrated by us in a multicellular organism *in vivo*. The results of these studies formed the basis of our proposed neurochemical concept of hormone-neurotransmitter imprinting in the developing brain.

The crucial role of norepinephrine for natural brain development in males was found out in our experiments on castrated males bearing transplanted fragments of immature rat ovary in the anterior chamber of the eye. Normally, estrogens in blood circulation of mature male rats are unable to induce hypophyseal luteinizing hormone surge similar to what happens in females. During SDB, fetal testosterone reprograms the brain development, originally determined by the female type, and the hypothalamus becomes refractory to estrogen. However, if newborn males are injected with a norepinephrine synthesis blocker,  $\alpha$ -methyl-*p*-tyrosine, luteal tissue appears in ovarian transplants and no cysts were found, which indicates the female type of hypothalamic-pituitary regulation of the ovaries.

In parallel with the SDB, the programming of HPAA takes place under the influence of maternal corticosteroids, which easily cross the placental barrier. An imbalance of corticosteroids of endogenous or exogenous origin disrupts the formation of fetal HPAA, which is found in the adult period of life. There are clinical observations that early use of corticosteroids has long-term adverse effects on neurodevelopment and HPAA function.

In experiments on Wistar rats, we studied the association of corticosteroid-induced HPAA programming disorders in terms of gender differences and in association with SDB [7, 9]. It turned out that catecholamines are the link between these processes.

Although corticosterone is the main glucocorticoid in rats, hydrocortisone was used in the experiments, because it is very close to corticosterone in terms of hormonal activities. Hydrocortisone acetate (HA) was administered to pregnant dams for the last week of gestation that caused their blood plasma corticosterone levels to rise by 53% on the final day. The use of SAA as an early marker of SDB disorder made it possible to detect its disorders in fetuses already at postnatal day 10. Enzyme activity in female offspring increased significantly in the POA that attenuated its sexual difference between males and females. In medial basal hypothalamus, prenatal HA led to impairment of formation of 5 $\alpha$ -reduced metabolites of testosterone.

In female pups, prenatal HA caused a decrease in norepinephrine levels in the POA with no changes in males resulting in disappearance of sex difference. This is likely due to the known effect of hydrocortisone inhibition of tyrosine hydroxylase in developing brain. At the same time, the rate of norepinephrine turnover in the POA of newborn males was increased. Prenatal HA caused an appearance of sex difference in the concentration of 5-hydroxyindolacetic acid, and serotonin metabolism in the POA, due to an increase of these parameters in females.

A change in the morphology of the suprachiasmatic and medial preoptic nuclei of the hypothalamus was also a manifestation of disturbed sexual dimorphism. Prenatal HA induced reduction of the neurocyte nuclei size in the suprachiasmatic nuclei of males to that of normal females. Perhaps this is a reflection of the violation of the

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programming the male sexual behavior, which is disturbed under the influence of prenatal HA, as well as the fertile potential.

On unanesthetized and unrestricted adult offspring, we have found that prenatally HA-exposed adult males, unlike females, do not respond to infusion of norepinephrine into the third brain ventricle by significant corticosterone rise in blood plasma. This was associated with the lack of stress-induced decline in the level of hypothalamic norepinephrine and increased synthesis of GABA. Contrary, experimental females demonstrated moderately enhanced HPAА and norepinephrine stress response.

Similar to HA, prenatal dexamethasone caused disorders of SDB eliminating sex difference of SAA in developing POA. Therefore, it is not surprising that males demonstrate abnormalities of sexual behavior in adulthood. HPAА and norepinephrine responses to restriction stress were similar to that of induced by HA.

The results of studies indicate the need for limited use of corticosteroids for the prevention of fetal distress syndrome with the threat of preterm birth.

A large part of our research was devoted to the prenatal stress syndrome (PSS) in male rats and other rodents born to stressed pregnant mothers. PSS is characterized by a low copulatory activity, homo- and bisexual behavior in adulthood and other abnormalities. G. Dörner and co-workers were doing such kind of research, and they were the first to obtain evidences that PSS is present in real human life [16-18].

We have shown that the restriction of pregnant rats during the last week of pregnancy leads to deficiency of SAA and changes in sex-specific protein distribution in the POA of newborn male offspring, as well as to reduction of the volumes of neuron nuclei in the medial preoptic and supra-chiasmatic nuclei. Next, we found out changes in the concentrations and metabolic turnover of catecholamines in the brain, and these changes are the predictors of violations in the direction of the brain demasculinization. Those disorders could be induced by prenatal  $\beta$ -endorphin and prevented by prenatal naltrexone, opioid receptor blocker, which indicate involvement of opioids in the brain demasculinization. Prenatal nimodipine, calcium ion blocker, normalized male sexual behavior in PSS and prevented modification of

the HPAА stress-responses. Obviously, calcium signaling plays an important role in the pathogenesis of PSS. Various manifestations of PSS could be prevented by prenatal use of dexamethasone,  $\beta$ -phenyl- $\gamma$ -aminobutyric acid (GABA antagonist), and methyl dopa.

The impact of endocrine disrupting chemicals as environmental pollutants on the developing brain organization have been in the circle of scientific interest of many investigators. We have contributed to the study of this issue in relation to the potential risk of exposure of the fetus to low doses of dibutyl phthalate and bisphenol A at SDB time window (15-21 gestation days). Dibutyl phthalate and bisphenol A can transfer across the placenta [19, 20].

The dose of dibutyl phthalate we used (100 mg/kg b.w. /day) was close to NOAEL (no observable adverse effect level) for rats (the NOAEL for developmental toxicity of dibutyl phthalate was established based on pup body weight and reproductive lesions at 50 mg/kg b.w. /day) [21]. As a result, we have discovered the phenomenon of prenatal dibutyl phthalate-induced hyperactive sexual behavior in young male offspring accompanied by a twice-increased level of testosterone in blood plasma. The hyperandrogenic status was then replaced by an accelerated involution of the reproductive system, including weakened male sexual behavior, androgen deficiency, oligospermia, etc.

Low doses of prenatal bisphenol A (25 mcg/kg b.w. /day), which was 200 times less of NOAEL for rats (5 mg/kg b.w. /day) [22], did not cause teratogenic effects, but adult male descendants demonstrated almost complete suppression of copulatory components of male sexual behavior, meanwhile testosterone level was preserved. After orchietomy and priming with estradiol and progesterone, they expressed lordosis behavior on contact with normal males. Histological and karyometric characteristics of the medial preoptic nuclei showed a decreased activity of neurocytes, which correlated with weakened male sexual behavior. Probably, the violation of SDB is due to the antagonistic action of bisphenol A against testicular testosterone of the fetus because of estrogen-like activity of the disruptor.

Our recent studies have looked at ibuprofen as a possible etiological agent that interferes with SDB programming. Ibuprofen, a widespread inhibitor of prostaglandin synthesis, is used as an

anti-inflammatory and analgesic drug. Although it is contraindicated in pregnancy, in real life many pregnant women take ibuprofen. The majority of pregnant women in the Western world report intake of mild analgesics, and some of them exhibit antiandrogenic properties [23]. In the USA and Great Britain, ibuprofen is one of the most frequently used analgesics by pregnant women with up to 18-28% reporting use [24,25].

In adult male rats, prenatally exposed to ibuprofen, a weakening of copulatory behavior was found by us without a change in sexual behavior according to the female type. Prenatal use of ibuprofen caused oxidative stress in the testis and the prostate of rats.

Research in the field of functional teratology remains relevant and will be continued.

## Conclusions

The research findings indicate the importance of further research in the field of so-called functional teratology. They are the pathogenetic basis for the prevention of a number of neuroendocrine and behavioral disorders.

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## Abbreviation

HA — hydrocortisone acetate

HPA — hypothalamic-pituitary-adrenal axis

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**NAF** — neonatally androgenized female rats

**NOAEL** — no observed adverse effect level

**PND** — postnatal day

**POA** — preoptic area

**PSS** — prenatal stress syndrome

**SAA** — steroid aromatase activity

**SDB** — sexual differentiation of the brain

## Наш півстолітній пошук розуміння етіології та патогенезу порушень розвитку нейроендокринної регуляції репродукції та ендокринної реакції на стрес (міні-огляд)

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**Резюме.** В оглядовій статті підсумовані основні результати півстолітніх експериментальних досліджень Відділу ендокринології репродукції та адаптації в галузі вроджених вад нейроендокринної системи, зумовлених патогенними впливами на материнський організм під час критичних періодів індивідуального розвитку. Досліджено патогенез перинатальних порушень формування нейроендокринних систем репродукції та адаптації, ендокринних та поведінкових наслідків цих порушень у віковому аспекті. Запропоновано нейрохімічну концепцію андрогензалежних розладів статевої диференціації мозку, які стосуються регуляції оваріальних циклів, статевої поведінки, функції гіпоталамо-гіпофізарно-адреналової системи та її реакції на стрес. Показана роль кортикостероїдів у ранньому програмуванні гіпоталамо-гіпофізарно-адреналової системи внутрішньоутробного плоду та виявлено аномалії її реакції на стресогенні чинники в дорослому житті експериментальних тварин. Розкрито нейрогормональні механізми патогенезу синдрому пренатального стресу, зокрема роль гаммааміномасляної кислоти і катехоламінергічної системи гіпоталамуса, і накреслено шляхи фармакологічної профілактики його негативних віддалених наслідків. Досліджено віддалені ефекти пренатальної експозиції до дибутилфталату, бісфенолу А та ібупрофену в якості ендокринних дизрапторів. Описано новий синдром гіперсексуальності та гіперандрогенії в самців щурів після експозиції материнського організму до низьких доз дибутилфталату протягом критичного періоду статевої диференціації мозку плоду. **Висновки.** Результати досліджень свідчать про важливість подаль-

ших пошуків у галузі так званої функціональної тератології. Вони є патогенетичною основою для профілактики низки розладів нейроендокринної регуляції та поведінки.

**Ключові слова:** мозок, статева диференціація, нейроендокринна система, пренатальний стрес, статева поведінка, ендокринні дизраптори, щури.

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