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## Neuroendocrine Disrupters

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## Neuroendocrinology

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Rennes, November 4<sup>th</sup>, 2023

Dear Editor, cher David,

You will find enclosed the Editorial for the special issue on Neuroendocrine disrupters. As previously discussed, this editorial introduces the importance of investigating the neuroendocrine system and its sensitivity to endocrine disrupters and briefly describes the manuscripts submitted and accepted in this special issue. I also highly the importance of using various methodological and multidisciplinary approaches, including epidemiology, “omics”, alternative to animal experimentation,... with the hope of providing AOP and strong data to support regulatory decisions.

I hope that you will find this manuscript appropriate for publication in “Neuroendocrinology”.

With my best regards



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Professor

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**Accepted manuscript**

Editorial: Neuroendocrine disrupters

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The strong interaction between the brain and the endocrine system is fundamental for the organism's survival and reproduction. The brain is able to modulate hormonal secretions, indirectly via the modulation of peripheral endocrine gland, or directly, via the production of its own neurohormones. In return, the brain is a prime target for hormones such as steroids, thyroid hormones, or growth hormones to name a few endocrine signals. Exposure to hormones, originating from the periphery or synthesized locally, will strongly impact brain functions and behavior through neuronal remodeling, or neuroplasticity. The impact of hormones on brain neuroplasticity can be reversible and happen at almost any time throughout life, a process called activation, or the consequences can be very long lasting, irreversible on some specific aspects of brain plasticity if hormonal exposure happens during a specific temporal window (development, but also to some extent puberty and probably menopause). This later action is called organization. Neuroendocrine systems such as the hypothalamus and the limbic system are among the most sensitive and the best studied structures in the brain due to high abundance of receptors involved for example in hypothalamic-pituitary regulation, the central control of energy balance and homeostasis in general, and reproductive and social behaviors. But the rest of the brain, including the thalamus, the mesencephalon, the cortex and the cerebellum to name a few brain regions, are strongly influenced by circulating hormones as well. Importantly, hormones exert their effects at extremely low concentrations, often down to the picomolar and femtomolar range, particularly during sensitive periods of life. Therefore, any interference with the endocrine pathways will impact brain and behavior and hence the survival or the reproduction of the individual and the species. The term endocrine disrupter (or endocrine disrupting compound; EDC) was coined more than 30 years ago during the Wingspread Conference in Wisconsin, USA (see [1] for historical perspective) and was later formalized by various scientific societies and governmental agencies such that an endocrine disrupter can be broadly defined as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" [2]. Importantly, "endocrine disrupters produce harmful effects in both humans and wildlife", requiring knowledge of the organism's biology. While the term "endocrine disruptor" and the acronym EDC are now commonly used, including by the general public, characterizing the potential deleterious impact of exogenous, anthropogenic or natural molecules, on the neuroendocrine system and consequently the behavior, remains a challenge, both for scientists and regulatory agencies. The study of EDCs is an interdisciplinary approach, from chemistry to epidemiology and back, to characterize how exogenous chemical factors influence the biology of living organisms through endocrine-related consequences. Knowledge gaps still exist and reliable, standardized, testing is necessary to identify endocrine disruptors, with the hope that regulatory agencies can use scientific knowledge and methods that are currently available to better predict and respond to public health crises associated with EDCs. The goal of the current special issue on

neuroendocrine disruptors is to bring additional information and open avenues to study the potential endocrine disrupting activities of chemicals on organisms. Obviously, the characterization of potential endocrine disrupting activities of chemical on the neuroendocrine system and behavior first requires the basic knowledge about the effects of endogenous hormones on target neuroendocrine systems. Lupu and her colleagues [3] provide a general review on how endogenous androgens and estrogens affect neuroplasticity, including neurogenesis, in the hippocampus, leading to consequences on learning and memory. Based on this fundamental biological knowledge, the authors review how several man-made chemicals, including bisphenols, phthalates, triclosan and several pesticides (or crop-protection products) can alter the endocrine signaling, not only via interference with hormone receptors, but also via an impact on the peripheral and local steroidogenesis. This review highlights the need for further research on long term consequences of early or late exposure to physiological level of endogenous hormones on the hippocampus and the consequences on the learning and memory processes before investigating the impact of EDCs on these mechanisms. A second review, from Ducroq and colleagues [4] focuses on the impact of phthalates on several brain regions and the underlying behaviors sensitive to androgens. Initial work rightfully focused on developmental impact of phthalates on reproductive behavior but more recent work, reviewed in this article, shows an impact, at very low doses (close to environmental concentrations), not only on the hypothalamus but also other brain regions, including the hippocampus. Furthermore, a growing body of evidence cited in the article show that the temporal window of exposure (juvenile, puberty, or adulthood) is a major factor to consider when investigating the potential impact of endocrine disruptors. And last but not least, Ducroq and colleagues show that phthalates can have an impact not only on neuronal networks but also on other tissues in the neuroendocrine systems, including the blood brain barrier. The reduction of circulating androgens or blocking the androgen receptors significantly alters blood brain barrier integrity. This is an important point as any disruption of this barrier will weaken the protection against other chemicals (including other EDC) and pathogens. Phthalates are therefore not only affecting the neuroendocrine system directly but also indirectly through increasing brain exposure to other drugs and chemicals and it is fundamental to investigate the whole breadth of actions of (neuro)endocrine disruptors to better comprehend the impact of these chemicals and their adverse effects.

When investigating the potential endocrine disrupting activities of chemicals, one approach is to define if some of the molecules released in the environment, from recent or older, acute or chronic, human activity are found in the organisms (human but also wildlife) and whether the presence of the molecule(s) is associated to (neuro)endocrine alterations. The article from Tillaut et al. [5] has taken this epidemiological approach and showed some negative correlation between the concentration of

some persistent organic pollutants (POPs), including polychlorobiphenyls (PCBs), organochlorine pesticides (OCPs) and per- and polyfluoroalkyl substances (PFASs) in 12-years old children (boys and girls) and the concentration of serum thyroid hormones (TSH, free T3 and free T4). Interestingly, the correlation between POP exposure and serum thyroid hormones was modified with pubertal stage, especially in boys. This type of epidemiological study is fundamental to determine environmental exposure in human and provides valuable information for risk assessment. A question often raised with the measurement of chemicals in the organism is the biological matrix, i.e. amniotic fluid, urine, serum, umbilical cord blood, hair or even teeth and sweat, as each matrix is potentially linked to a temporal pattern of exposure, that needs to be linked to the substance's toxicokinetic. False negative, especially linked to early, developmental exposure, is therefore a major obstacle. But once their presence is attested and quantified, their association with endocrine-disrupting activities needs to be causally tested using laboratory models. An example of the consequences of early exposure to PCB, here Aroclor 1254, on neuroendocrine dysfunction is provided by Pinson and her Colleagues [6]. Using a mouse model, they show that early maternal exposure to Aroclor 1254, a commercial mixture of polychlorinated biphenyls (PCBs) associated with alterations of cognitive functions in children [7] and altered levels of thyroid hormones (this issue and [4]), has a significant and cell-type specific impact on neurogenesis in the hippocampus later in life. Indeed, newborn neurons were specifically affected while mature granules cells were not. Methodological approaches used here are relatively unique as newborn dentate granule cells of the hippocampus were specifically isolated from transgenic mouse using flow cytometry and transcriptome analyzed by RNA sequencing. Further targeted experiment on these newborn neurons showed an alteration of mitochondrial and synaptic functions, likely linked to a disruption of thyroid hormone pathways. This type of work is fundamental as it adds information on the differential sensitivity of various cell types to neuroendocrine disruptors and confirms the need for a better understanding of fundamental mechanisms of cell physiology and brain neuroplasticity. Omics methodologies were also applied to investigate the impact of the flame retardant FireMaster® 550 (FM 550) or its individual brominated (BFR) and organophosphate ester (OPFR) on the cortex (Witchey et al., [8]). Flame retardants are found in various everyday life objects, including furniture and electronics. A new, comprehensive approach was taken by the authors to investigate the consequences of this exposure on neonatal cortex on a global scale by using a combination of transcriptomic and lipidomic techniques. While the use of transcriptomic methodologies to study the biological impact resulting from EDC exposure is increasing, the consequences of potential enzymatic alteration resulting from change in RNA transcription is seldom investigated. The authors show that the neonatal (PND1) cortex transcriptome is, not surprisingly, highly sexually dimorphic, but they also show that lipid composition is also strongly determined by sex. Witcher also highlight multiple adverse modes of action with a strong impact on ceramides and sphingomyelin for the BFRs and OPFRs and males are more

significantly impacted by OPFR exposure. The discovery that the lipid composition of the postnatal cortex is so highly sexually dimorphic, provides additional and novel insight as to how and why the male and female brain respond differently to environmental exogenous exposures and stresses. The endocrine pathways are not clearly defined but could involve RXR and LXR as well as ERs. Furthermore, long term consequences of such alteration and the potential adverse effects on the organism remain to be investigated.

One can also see from these above studies and reviews that a strong emphasis is made to investigate neurodevelopmental impacts of EDC as important parameters in Developmental Origins of Health and Disease (DOHaD). Exposure protocols often involve exposure of pregnant or lactating dams to chemical and the impact on the mother themselves are almost never investigated. The physiological changes associated with pregnancy, particularly at hormonal level have a major impact on many pharmacokinetic parameters. Given that half (and even a little more) of the human population is female, and that approximately 80% of women will at some point in their lives become pregnant at least one time, it is more than essential to define the potential impact of EDC on female's physiology and brains during gestation and/or lactation, in addition to knowing what impact these molecules might have on the development of newborn babies (see further discussion in [9]). In this special issue, Bonaldo and colleagues [10] studied the impact of bisphenol BPA and its analogue BPS on the neuroendocrine system and on maternal behavior, suggesting that alterations in maternal care may affect the offspring physiology and behavior. They show that BPA- and BPS-treated mouse dams spent significantly less time taking care for the pups compared to the controls and this likely resulted in the offspring survival and difference in sex ratio. In parallel, the expression of oxytocin is also affected in the paraventricular and supraoptic nucleus in BPA-treated dams. These impact on the mother should be kept in mind while investigating the impact of potential EDC on offspring physiology and behavior.

Direct EDC exposure during key temporal windows, early development but also during puberty and pregnancy, changes the brain neuroplasticity and subsequently, behavior and cognition of the exposed individuals. While these approaches on animals are mandatory to define deleterious consequences on reproduction or survival, the development of screening tests to assess the potential impact of the thousands of man-made molecules found in the environment is essential. Using the XETA test (Thibz:eGFP tadpoles OECD test guideline N° 248) to highlight disruption of thyroid hormone pathway, Spirhanzlova and colleagues [10] report that the exposure to very low concentrations (down to  $10^{-10}$ M) of chlorpyrifos, a cholinergic neurotoxicant at medium to high concentrations, is associated with numerous neurodevelopmental effects independent of cholinergic alterations. Using various techniques, including electron microscopy, they showed that axon myelination was significantly impacted. It should be noted that an increasing number of in vitro tests, including tests on early



developmental stages in xenopus and zebrafish (EASZY assay, OECD test guideline N°250) are validated to highlight endocrine disrupting activities of chemicals. Further development of alternative approaches to animal experimentation is required but to do so, we need to really understand the global impact of hormones on the organism as a whole and to assess the consequences of the disruption on neuroendocrine pathways. This information can then be used to construct Adverse Outcome Pathway (AOP), a sequential chain of causally linked events, also called key events from molecular target to cell, tissue, organism and then on the population and the species. Defining a disruption of this chain of events linked to adverse effects is the central element of a toxicological knowledge framework to support chemical risk assessment. The basic, fundamental, knowledge of the biological mechanisms is first required to define the key events potentially affected by endocrine disrupters. Once biological targets are identified, standardized in vitro assays can be developed and validated to test old, persistent, and new chemicals (for example REACH).

It is important to note too that, while studies on neuroendocrine disruption have focused mostly on impact through estrogens, androgens and thyroid hormones pathways, there is still little known on the potential disruption by environmental chemicals of other endocrine pathways, such vitamin D, retinoic acid, growth hormone and glucocorticoids. In addition, the brain itself is able to produce its own hormones, especially steroid hormones such as androgens and estrogens. The biological impact of this local synthesis, and metabolism, is still not entirely known, making difficult to interpret the consequences of endocrine disrupters on neuroendocrine systems.

Altogether, standardized methodologies, including multiomics approaches and behavioral paradigms, will help defining neuroendocrine disrupters. We need to keep in mind the numerous variables, including developmental stages, sex, combination of hormonal pathways to name a few, when studying the neuroendocrine pathways. But at the end, only standardized and validated methodologies will help in the assessment of danger and risk of exposure to chemicals, and lead to the regulation of harmful chemicals.

Conflict of Interest Statement: None

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