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When pharmaceutical drugs become environmental pollutants: Potential neural effects and underlying mechanisms

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ABSTRACT

Pharmaceutical drugs have become consumer products, with a daily use for some of them. The volume of production and consumption of drugs is such that they have become environmental pollutants. Their transfer to wastewater through urine, feces or rinsing in case of skin use, associated with partial elimination by wastewater treatment plants generalize pollution in the hydrosphere, including drinking water, sediments, soils, the food chain and plants. Here, we review the potential effects of environmental exposure to three classes of pharmaceutical drugs, i.e. antibiotics, antidepressants and non-steroidal anti-inflammatory drugs, on neurodevelopment. Experimental studies analyzing their underlying modes of action including those related to endocrine disruption, and molecular mechanisms including epigenetic modifications are presented. In addition, the contribution of brain imaging to the assessment of adverse effects of these three classes of pharmaceuticals is approached.

1. Introduction

Human and veterinary medicine uses a large variety of pharmaceutical drugs and their consumption can reach several thousands of tons in some countries (Hider-Mlynarz et al., 2018; Ortiz de García et al., 2013; Van Boeckel et al., 2014). The hepatic route leads to their partial conjugation (glucuronidation, sulfation, methylation, for elimination) leaving a proportion of pharmacologically active molecule in urine and/or feces during their elimination (Kokki, 2010; Lucas, 2016; Rainsford, 2009; Verbeeck et al., 1983). Pharmaceutically active compounds and their metabolites are not completely eliminated by wastewater treatment plants transforming them into environmental pollutants (Aemig et al., 2021; Bisognin et al., 2020; Chiffre et al., 2016; Lonappan et al., 2016). At the worldwide level, pharmaceutical drugs are detectable in surface and ground water with a transfer in sediment and soil showing a global environmental contamination (Ahkola et al., 2017; aus der Beek et al., 2016; Awad et al., 2014; Besse and Garric, 2008; Charuaud et al., 2019; Desbiolles et al., 2018; Ortiz de García et al., 2013; Wang et al., 2017).

In many species, brain development and function are dependent on internal factors including steroid and thyroid hormones (Coumailleau et al., 2015; Duarte-Guterman and Trudeau, 2010). In mammals, neurogenesis, cell migration and neuro-glial differentiation in the cerebral cortex, hippocampus and hypothalamus are mediated by sex steroids and thyroid hormones (Adhya et al., 2018; Parent et al., 2011; Zoeller et al., 2002). During development, the sexual differentiation of the brain is regulated by sex steroids through the masculinization of several brain areas including the preoptic area (POA), a sexually dimorphic region of the hypothalamus regulating sexual behavior in male and maternal behavior in female (Schwarz and McCarthy, 2008a). At the adult stage, sex steroids play a crucial role in reproductive function since they trigger the puberty and control the neuro-glial Gonadotropin-Releasing Hormone (GnRH) and kisspeptin networks (Delemarre et al., 2008; Nestor et al., 2018; Vigil et al., 2011). This dependence on steroids and thyroid hormones makes the brain a target for molecules with endocrine disrupting activity during perinatal stage and adulthood. In addition, thyroid hormones also target the brain through their involvement in maturation phases. In particular, they have a crucial role for the

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myelination and myelin turnover (Calzà et al., 2015). Moreover, recent studies show that thyroid hormones play an important role in microglial development (Rousseau et al., 2020).

Many of the pharmaceutical drugs, which are now considered also as environmental pollutants, exert their therapeutic action by interacting with the endocrine system and for many of them, with neural cells.

The benefits of pharmaceutical drugs as therapeutic agents is no longer to demonstrate. These molecules undergo both pre-clinical and clinical trial phases before their marketing, consisting in toxicologic assessments to evaluate potential risks (carcinogenicity, genotoxicity, reproductive toxicity …) according to the guidelines proposed by the International Council on Harmonization or ICH (Goineau et al., 2013; "https://www.ich.org/," n. d.) for human pharmaceuticals and VICH for veterinarian compounds (https://vichsec.org/en/). The adverse impact of candidate drugs on the central nervous system (CNS) are evaluated during the pre-clinical phase in accordance with three guidelines: i) the guideline S7A (safety pharmacology studies) with behavioral tests after a single injection of the pharmaceutical candidate in adult animals, ii) the Pre- and Post-Natal development (PPND) study of the guideline S5 (R3) (reproductive toxicology) with behavioral tests after developmental exposure, from E6 to PN21 in rat (from the 6th day of embryonic (E) development to the 21st Post-Natal (PN) day) and iii) the guideline S11 or Juvenile Animal Study (JAS) for the assessment of potential toxic effects on neonate, infant, child and/or adolescent with behavioral tests, learning and memory tests and neuro-histopathology evaluations. These regulatory assessments do not evaluate adverse effects of pharmaceutical drugs at neuroanatomical, cellular or molecular level (Barrow, 2018; "https://www.ich.org/page/safety-guidelines," n. d.). Only very few studies reported the impact of these candidate molecules as environmental pollutants. Nevertheless, an environmental risk assessment has to accompany an application for a marketing authorization for a pharmaceutical. It consists in the determination of the Predicted Environmental Concentration (PEC) of the drug substance in surface water and the evaluation of adverse effects (if the PEC exceeds 0.01 μg/L) on algae, Daphnia and fish (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf).

The aim of this article is to review the potential adverse effects of three categories of pharmaceutical environmental pollutants: the antibiotics, the antidepressants and the anti-inflammatory drugs, on the development of the central nervous system (CNS) in mammals. These three categories of pharmaceuticals were chosen according to the following criteria: i) they are largely consumed, ii) they are quasi-systematically listed in dosing studies reported in the scientific literature and iii) they are huge environmental contaminants and notably for the hydrosphere. The mechanisms underlying the potential endocrine disrupting effects of these pharmaceuticals will be discussed. Since a delay exists between the exposition during development and the manifestation of the adverse effects, at adult stage, we will expose the implication of epigenetic modifications that may account for such delayed effects. Finally, we will briefly introduce the potential of neuroimaging techniques for measuring and following the endocrine changes induced by pharmaceutical agents.

2. Neural effects of exposure to antibiotics

Antibiotics are widely used in human medicine and most importantly in veterinary medicine and agriculture (Jechalke et al., 2014; Machowska and Stålsby Lundborg, 2018). Therefore, their emission in the environment is mainly due to human sources (hospital waste, and wastewater treatment plant …), and to a larger extent to agricultural uses as therapeutic molecules but also as promoters of animal growth (Puckowski et al., 2016). Previous research highlighted the worldwide presence of antibiotics, with regional differences among the five analyzed regions across Eastern and Western Europe, Asia, Africa and America (aus der Beek et al., 2016). Studies monitoring the occurrence of pharmaceutical substances detected antibiotics in wastewater treatment plants, surface water, groundwater sediments and aquatic species including invertebrates and vertebrates (Ahkola et al., 2017; Awad et al., 2014; Charuaud et al., 2019; Chiffre et al., 2016; Guo et al., 2021; Ortiz de García et al., 2013; Wee et al., 2021; Xie et al., 2017). The resulting measured concentrations in the environment vary from nanograms or micrograms to milligrams, with seasonal variations and higher concentrations in winter than in summer (Awad et al., 2014; Kot-Wasik et al., 2016).

In mammals, the neural effects of antibiotics were mainly studied in the context of therapeutic use. Encephalopathy, optic neuropathy, seizures and peripheral neuropathy are some examples of undesirable neurotoxic side effects associated with their use (Koppel et al., 2001; Lamoth et al., 2009; Weinstein et al., 2009). It has been shown, in particular, that following therapeutic use certain antibiotics induced neurotoxic effects via the disruption of neurotransmitter release or the functional alteration of neurotransmitter receptors, the increase in glutamate levels, the release of cytokines in the brain as well as the modification of blood-brain barrier permeability (Chow et al., 2005; Fiekers et al., 1983; Sugimoto et al., 2003).

Fetal, postnatal and early childhood are critical periods for neural development. The disruption of the systems involved in brain homeostasis during these early periods of neurodevelopment can have long-term consequences. Future studies are needed to determine whether environmental exposure to antibiotics directly affects brain development or whether microbiome molecules that travel to the brain disrupt gene activity and cause cognitive deficits. In humans, a longitudinal cohort study showed that 70% of European children who received antibiotics in early life, but not during pregnancy, presented higher ratings of social difficulties, attention deficit hyperactivity disorder and depression symptoms at a later age compared to non-exposed children (Slykerman et al., 2017). It was shown in several mammalian studies that administration of high doses of antibiotics during critical periods of development induced long-term effects on brain and behavior by acting directly on the nervous system or indirectly through microbiota modifications (reviewed by Champagne-Jorgensen et al., 2019). In rodents, pre-breeding and/or gestational exposure to one antibiotic (1% succinylsulfathiazole in diet) or to an antibiotic cocktail (5 mg/ml neomycin, 5 mg/ml bacitracin and 1.25 μg/ml pimaricin in drinking water) elicited changes in social and emotional behaviors (Degroote et al., 2016; Tochitani et al., 2016). In agreement with this study, it was recently shown that perinatal exposure of mice to a relatively low-dose of penicillin (31 mg/kg/d) induced long-term modifications in the cortical cytokine expression, blood–brain barrier integrity, and behavior (Leclercq et al., 2017). In particular, antibiotic-treated offspring exhibited impaired anxiety-like, social and aggressive behaviors.

The cellular and molecular mechanisms reported for antibiotics are briefly summarized here. Several scientific studies using electrophysiology have shown that some of these antibiotics interfere with the glutamatergic and/or gabaergic systems. These interactions had been demonstrated in the past for all quinolone antibiotics, such as norfloxacin and ciprofloxacin, which inhibited the specific binding of ligands to GABAA and ionotropic glutamate receptors in a concentration-dependent manner, with an IC20 of 220–930 μM and 70–480 μM, respectively, in mammalian cells (Dodd et al., 1989; Halliwel et al., 1995). Given the importance of the gabaergic and glutamatergic systems in various processes of neurogenesis, this raises the question of the risk of chronic exposure to these antibiotics during development, due to environmental contamination. Otherwise, the neurotoxic effects of some quinolones in combination with certain non-steroidal anti-inflammatory drugs enhanced the inhibitory potency of ciprofloxacin by approximately 3000-fold (100 μM versus 0.03 μM) as previously reported (Halliwel et al., 1995).

Another cellular mechanism that was widely reported for the neural effects of antibiotics involves microglia. It has been established for several years that certain antibiotics, such as tetracyclines or

minocycline, have an inhibitory action on microglial cells, the immune cells of the central nervous system (Schmidtner et al., 2019; Scott et al., 2018; Tikka et al., 2001). Recent studies demonstrated that microglial activation is not only a hall-mark of neuroinflammation, but plays important roles during brain development. Inhibition of microglial activation by minocycline was shown to induce extensive neuronal cell death and impair neurogenesis in the subventricular zone (SVZ) and synaptic pruning in the early postnatal and adolescent rodent brain, respectively (Inta et al., 2016). These deleterious effects contrast with the neuroprotective actions of minocycline at adult stages (Arnoux et al., 2014; Liu et al., 2017; Ueno et al., 2013).

It has been reported in mammals that catalase and glutathione s-transferase are also modulated by tetracycline in some organs, including the brain (Satpute et al., 2017; Turkan et al., 2020). It is of particular interest to note that these two enzymes are important in microglial cells to promote pro-inflammatory astro-microglia communication (Kano et al., 2019). Therefore, changes in microglial function could trigger important brain disturbance if exposure to antibiotics occurs during developmental periods.

Neural effects of exposure to antibiotics were also reported in aquatic models, which with other wild life represent good sentinels for the environmental contamination (Animals as Sentinels of Environmental Health Hazards, 1991). Exposure of zebrafish to norfloxacin (600, 900 and 1200 mg/L) affected not only the hatching rate, increased mortality and malformation rate of the embryos, but also inhibited the expression of glial (Glial fibrillary acidic protein or GFAP), stem cell (sex determining region Y-box 2 or sox 2) and mature neuronal (enolase 2) markers (Xi et al., 2019). In addition, exposure to norfloxacin induced cell apoptosis in the brain of zebrafish embryos as evidenced by measurement of caspase 3 activity and expression ratio of Bcl-2–associated X (Bax) to B-cell lymphoma 2 (Bcl 2). The apoptotic phenotype was rescued by administration of MK-801, a noncompetitive antagonist of the N-Methyl-D-aspartate (NMDA) receptor, suggesting that the activation of NMDA receptors mediated the developmental neurotoxicity of this antibiotic. Another study focused on acute exposure effects of tetracycline (5, 50 and 500 ng/L), an antibiotic subclass representing the second highest frequency of detection in environmental matrices, in the freshwater fish Gambusi holbrooki (Nunes et al., 2015). The results suggested the existence of a cause-and-effect relationship between tetracycline exposure and antioxidant effects, neurotoxicity, histological alterations and glutathion-S-transferase, catalase and acetylcholinesterase enzymatic activities as described above in mammals.

The potential effects of antibiotics were also studied in the context of combined exposure with other environmentally detected pharmaceuticals. Liu et al. (2017) showed that combined exposure of Crucian carp to an antibiotic, erythromycin, at 2 μg/L and an anti-fungal molecule, ketoconazole, at 0.2, 2 or 20 μg/L inhibited acetylcholine esterase activity and swimming behavior and enhanced shoaling. Exposure of fish, *Astyanax bimaculatus*, to sewage effluents added with five pharmaceuticals including four antibiotics (ciprofloxacin at 11.44 μg/L, oxytetracycline at 7.93 μg/L, sulfamethoxazole at 188.69 μg/L, trimethoprim at 30.65 μg/L) and paracetamol at 151.17 μg/L increased glutathione-S-transferase activity in the brain (Bisognin et al., 2020).

Whether antibiotics found in the environment trigger neural adverse effects for human health and environment through endocrine mode(s) of action still needs a thorough investigation, in particular at environmental doses. However, some evidences in aquatic animals point out a possible alteration of neuroendocrine systems. Chronic exposure of Japanese medaka (*Oryzias latipes*) for 120 days to cefadroxil at 84.8 μg/L and cefradine since 73.9 μg/L impaired growth and reproduction (Kim et al., 2017). These effects were associated with altered expression levels of gnrh1, gnrh2, estrogen receptors (esr1, esr2), and cyp19 b in the brain (Kim et al., 2017). Modifications in the pituitary expression of gnrh1r and gnrh2r encoding GnRH receptors and in estradiol levels were also observed (Kim et al., 2017). In a previous study, the same group showed that chronic exposure of Japanese medaka to lincomycin at 0.42 mg/L significantly reduced juvenile survival at 30 day post-hatch (Kim et al., 2012). Interestingly, exposure to lincomycin also increased vitellogenin levels in male fish at 90-day post-hatch. In the same study, exposure of human adrenal cells to lincomycin also altered steroidogenesis and increased estradiol concentrations. In accordance with these data, another antibiotic, ciprofloxacin has been previously reported to inhibit the activity of cytochrome P450, a key enzyme in hormone synthesis, in rat and human (Granfors et al., 2004; McLellan et al., 1996). Besides these studies reporting alterations in the gonadotropic axis and/or in steroidogenesis, thyroid disruption was also observed in a study addressing long-term exposure of Zebrafish embryos to environmentally relevant concentrations of oxytetracycline (1000 or 5000 ng/L) from 2 h to 120 d post-fertilization (Yu et al., 2020). In particular, exposure to oxytetracycline increased triiodothyronin concentrations, reduced levels of thyroid stimulating hormone, and affected growth and development of Zebrafish. From these studies, it appears that relatively low doses of antibiotics can exhibit endocrine modes of action in aquatic models, through impairment of the gonadotropic or the thyroid axes. This raises the question of the potential adverse effect on the nervous system, given the importance of thyroid and sex hormones in neural processes during critical periods of development.

3. Effects of antidepressants on CNS development

Numerous psychiatric pharmaceuticals are widely prescribed to treat mental illnesses such as depression, psychosis, anxiety, epilepsy or mood disorders. Therefore antidepressants constitute one of the most commonly prescribed drugs in developed countries (France, Aemig et al., 2021; Spain, Ortiz de García et al., 2013; USA, Pratt et al., 2017; reviewed by Castillo-Zacarías et al., 2021). The growing consumption of antidepressants is associated to a growing occurrence of these drugs in urban waters as well as in rivers and oceans (aus der Beek et al., 2016; Martin et al., 2019; Mole and Brooks, 2019; Saaristo et al., 2019), leading to an emerging environmental contamination by antidepressants. Antidepressants act directly on brain's biochemistry by modifying neurotransmitter metabolism. Various classes of antidepressants implicate different mechanisms of action within the CNS, regulating notably the serotonin neurotrophic effects. Each class is identified according to its mechanism of action on neurotransmitters: the selective serotonin reuptake inhibitors (SSRIs), which are the most widely prescribed (Kulikov et al., 2018); the serotonin and norepinephrine reuptake inhibitors (SNRIs); the serotonin modulators and stimulators (SMSs); the serotonin antagonists and reuptake inhibitors (SARIs); the noradrenergic and selective serotoninergic antidepressants (NaSSAs); the norepinephrine reuptake inhibitors (NeRIs); the serotonin, norepinephrine and dopamine reuptake inhibitors (SNDRIs) or triple reuptake inhibitors (TRIs); and the melatonin and serotonin agonists (MaSAs) (Fitzgerald and Watson, 2019). SSRIs are mainly prescribed for treating major depressive disorder, and particularly perinatal depression (Latendresse et al., 2017). Among them, fluoxetine (Prozac®) is metabolized by cytochrome P-450 isoenzymes to norfluoxetine, which retain the pharmacological activity (Mandrioli et al., 2006). This active metabolite is eliminated in the urine and then disseminates into wastewaters. Fluoxetine and norfluoxetine are widely detected into various environmental compartments such as surface, ground, marine and drinking waters, soils and sediments in the range of ng/L to mg/L (Biel-Maeso et al., 2018). In the United Kingdom, fluoxetine can be detected in drinking water at low concentrations (0.27 ng/L; Peng et al., 2019). In this review, fluoxetine is taken as an example of SSRIs antidepressant that constitutes an environmental pollutant.

According to a report from the Organization for Economic Cooperation and Development (OECD) on pharmaceuticals consumption in 2019 (OECD iLibrary), the consumption of antidepressant drugs doubled in OECD countries between 2000 and 2017. Such an increase in human consumption generated an amplification in environmental contamination (reviewed by Castillo-Zacarías et al., 2021). Therefore

antidepressants constitute emerging environmental pollutants. Regarding the wide dissemination of antidepressants in the environment, numerous studies demonstrated deleterious biological effects on aquatic wildlife ecosystems due to antidepressant contamination in the environment (reviewed by Sehonova et al., 2018). Antidepressant dissemination in rivers, estuaries and coastal waters exposes aquatic organisms like fishes, amphibians or mollusks, leading to alterations in essential physiological and behavioral processes through neurological and neuroendocrine effects. For example, in eastern mosquitofish (*Gambusia holbrooki*), fluoxetine exposure at environmental doses alters antipredator and anxiety-related behaviors (Martin et al., 2017, 2019), as well as reproductive behaviors such as courtship and sexual partners interactions (Martin et al., 2019) or copulatory behavior (Bertram et al., 2018; Fursdon et al., 2019). In the meagre (Argyrosomus regius), Duarte et al. (2020) demonstrated alterations in fish growth, oxidative stress, detoxification mechanisms and lipid peroxidation in the liver (Duarte et al., 2020). Such results suggest an endocrine disruption mode of action implicating alterations within the hypothalamic-pituitary-adrenal (HPA) axis, the gonadotropic axis or the thyroid hormones regulation.

Beyond such effects disturbing aquatic wildlife ecosystems, antidepressant metabolites concentrate in brain and liver tissues (David et al., 2018; Pan et al., 2018), as well as in plasma, of fishes consumed by humans (Sims et al., 2020). Therefore, either through direct effects via drinking water or through indirect effects via aquatic food, environmental contamination by antidepressants may constitute a risk for human health.

Antidepressant drugs such as fluoxetine are commonly prescribed in women for treating major depressive disorder during pregnancy and/or postpartum depression. As these drugs cross the placental barrier (Arumugasaamy et al., 2019; Hendrick et al., 2003) and diffuse in breast milk (Schoretsanitis et al., 2019, 2020), and because of their action on neurotransmitter metabolism, antidepressants are expected to affect the developing fetal and postnatal brain of respectively fetuses and newborns. Then antidepressants may constitute a risk for human health as their potential disrupting effects during embryonic and postnatal brain development may alter development, growth and regulation of neural systems, as well as neural plasticity, with long-term consequences.

In rodents, developmental exposure to antidepressants during prenatal life and/or lactation has been demonstrated to induce long-term endocrine, behavioral and neural alterations. Most of the results are relatives to the control of the HPA axis. In mice, developmental fluoxetine exposure alters endocrine and behavioral response to stress in adult female and male progeny (Avitsur, 2017; Avitsur et al., 2016). Indeed prenatal fluoxetine exposure disrupts the negative feedback control of the HPA axis response to stress and reduces anxiety- and depressive-like behaviors at adulthood, that could be due to a glucocorticoid insensitivity. In rats, postnatal fluoxetine exposure up to weaning induces in male offspring only, at adult stage, an increase in anxiety-like behavior and impairments in HPA axis negative feedback (Gobinath et al., 2016). These impairments are associated with sexually dimorphic adult hippocampal neurogenesis alterations, since hippocampal neurogenesis is amplified in adult males after preweaning fluoxetine exposure and reduced in adult females. Otherwise, perinatal fluoxetine has been shown, in male rats, to decrease corticosterone levels, to increase both serotonin levels in the hippocampus and pre-synaptic density in the dentate gyrus (Gemmel et al., 2017), and to induce sexually differentiated effects on hippocampal neurogenesis and glucocorticoid receptor density (Gemmel et al., 2019). Moreover, on prenatally stressed progeny, developmental fluoxetine exposure modifies the dopaminergic system in the hippocampus and decreases monoamine levels (Gemmel et al., 2016). Decreases in hippocampal BDNF IV and its receptor TrkB mRNA expression after developmental fluoxetine exposure constitute other molecular processes that may be implicated in long-term programming effects on brain and behavior (Boulle et al., 2016).

Other studies reported fluoxetine-induced alterations within the reproductive function. In male mice, fluoxetine exposure during fetal development and lactation reduces at adulthood sexual motivation (Gouvêa et al., 2008). In rats, developmental fluoxetine exposure induces in adult male sexual behavior impairments (Rayen et al., 2013). Moreover, it decreases the area of the sexually dimorphic nucleus of the preoptic area (SDN-POA), implicated in rodents in the control of sexual behavior.

Comparable to fluoxetine, sertraline, a frequently prescribed SSRI, has been demonstrated to modify as well neuroendocrine and behavioral parameters in progeny of maternal exposure in rodents. In rats, Kott et al. (2019) described alterations in HPA axis secretions, anxiety behavior and cognition, with sex-specific effects in the adult offspring (Kott et al., 2019). Moreover, sertraline developmental exposure throughout gestation modifies permanently in adult mice the levels of serotonin receptors and transporters mRNAs in the cerebral cortex (Meyer et al., 2018).

Altogether, these results demonstrate long-term endocrine and behavioral, as well as neural, effects after prenatal and perinatal SSRIs exposure. The neural effects are suspected to be involved in endocrine and behavioral alterations, as some remodeling of neural circuits in early life are able to modulate behavioral responses at adulthood.

If literature reporting endocrine, behavioral and neural effects induced by developmental exposure to pharmacological SSRI doses is significant, in contrast literature related to human risk constituted by antidepressants exposure at environmental doses during pre- and perinatal development is poorly documented. We can notice that, through in vitro and in silico approaches using differentiated human neuroblastoma cells treated with a mixture of psychoactive pharmaceuticals including fluoxetine at environmentally relevant concentrations, Kaushik et al. (2016, 2017) identified alterations in neuronal gene expression associated with neurological disorders such as Autism Spectrum Disorders (ASD), Alzheimer's disease and schizophrenia. Among the genes exhibiting expression alterations, several genes coding synaptic proteins associated with ASD are affected (Kaushik et al., 2016, 2017).

Finally, it can be mentioned that some indirect effects may be suspected, implicating the gut microbiota. Gut microbial metabolites participate to homeostasis and development. If maternal SSRIs treatment modifies maternal microbiota, the progeny central nervous system may be the trigger of alterations with long-term consequences (Ramsteijn et al., 2020).

Therefore more studies using environmentally relevant doses are needed to evaluate the risk for human health of antidepressants environmental contamination. Technological progress is aiming to remove pharmaceuticals from sewage (reviewed by de Oliveira et al., 2020). If, over last years, such progress has improved, however, such as for most of pharmaceuticals, wastewater treatments remain only partially efficient in removing antidepressant molecules. Considering the diversity of pharmaceuticals detected in various environmental compartments, notably antidepressant molecules, triggering the CNS and neurotransmitter metabolism, cocktail effects have to be defined.

4. NSAIDs and neurodevelopment

Nonsteroidal anti-inflammatory drugs (NSAIDs) are pharmaceuticals that reduce pain, decrease fever and inflammation. Diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen and paracetamol (or acetaminophen) are the most common, they are free sold in numerous countries (Rayen et al., 2013). In 2010's approximatively 250 000 kg of ibuprofen were consumed in Germany, France, Spain; 1 065 000 kg and 3 300 000 kg of paracetamol were consumed respectively in Spain and France (Chiffre et al., 2016; Ortiz de García et al., 2013). Pharmacokinetic studies show that NSAIDs are excreted via urine and feces in conjugated and free forms (Lucas, 2016; Rainsford, 2009; Small, 1989). These metabolized and non-metabolized NSAIDs forms in addition to creams, gel and patch are not totally eliminated by wastewater

treatment plants (Wang et al., 2017). Therefore, NSAIDs are frequently dosed in the hydrosphere, sediments and soil showing a general contamination (Amalric and Togola, 2011; aus der Beek et al., 2016; Ortiz de García et al., 2013). The consequences of this general pollution is the contamination of the animal trophic chain, from phytoplankton to predators (Bean et al., 2018; Xie et al., 2017), vegetables (Wu et al., 2013) and drinking water. Indeed, contamination of drinking water is reported in several studies in multiple areas with maximum concentrations of 1350 ng/L for ibuprofen in United States, 166 ng/L for ketoprofen and 114 ng/L for diclofenac in Poland and 210 ng/L for paracetamol in France (Caban et al., 2015; Kot-Wasik et al., 2016; Mompelat et al., 2009; Togola and Budzinski, 2008). This generalized environmental contamination, outside the therapeutic context, leads to chronic human exposure to NSAIDs which physiological effects need to be documented.

NSAIDs exert their pharmaceutical action by inhibiting the activity of cyclooxygenases COX-1 and COX-2 enzymes (Brideau et al., 1996; Patrignani et al., 1997; Van Hecken et al., 2000). COX-1 and COX-2 are encoded by PTGS1 and PTGS2 (prostaglandin-endoperoxide synthase) genes respectively and catalyze the bis-dioxygenation and reduction of Arachidonic Acid to Prostaglandin E2 (PGE2), mediator of neuropathic pain (Ma and Quirion, 2008; Rouzer and Marnett, 2009). For the CNS pain, NSAIDs are largely prescribed or indicated in case of headache or migraine in adult and their toxicity were reported in case of overdose (Auriel et al., 2014; Becker, 2015; May, 2018). If adverse effects of NSAIDs are well identified in adult and if the communication exists to sensitize the consumers and to prevent CNS disorders, little is known about the effects of NSAIDs exposure during brain development. However, developmental exposure to NSAIDs exists as shown by several studies. First, placenta is not a barrier preventing NSAIDs fetal exposure since Siu (2000) demonstrated that after an administration of diclofenac to pregnant women before legal termination of pregnancy, this drug was measured in amniotic and coelomic fluids with a mean ratio of 0.95 for maternal plasma/fetal tissues. Fetal exposure was confirmed with the presence of ibuprofen, naproxen and indomethacin in the meconium of 101 infants in the Michigan (Alano et al., 2001). NSAIDs exposure is potentially prolonged to neonatal stage since ibuprofen and naproxen were measured in human breast milk at 0.37 μg/kg and 1.9 μg/kg respectively. In the same study, diclofenac was dosed at 0.09 μg/kg, ketoprofen at 0.15 μg/kg and naproxen at 0.35 μg/kg in powdered infant milk according the provenance (Azzouz et al., 2011). Knowing that NSAIDs inhibit the production of PGE2, we can ask ourselves if developmental exposure to NSAIDs has an impact on the brain differentiation.

PGE2 is involved in the development of specific brain areas and in particular in hypothalamus and cerebellum differentiation. Its four receptors, EP1 to EP4 (or PTGER1-4: prostaglandin E receptor) are not ubiquitously distributed in the CNS. In rat, maximum expression of EP1 is found in pituitary gland and cerebellum, in hypothalamus and pituitary gland for EP2, in thalamus and hypothalamus for EP3 and cerebellum and cortex for EP4 (Myren et al., 2012). Several studies showed a direct implication of PGE2 in the development of the cerebellum and the preoptic area (POA), a subdivision of the hypothalamus controlling masculinization of adult sex behavior (Schwarz and McCarthy, 2008b). Amateau and McCarthy (2002) show, using POA neurons of newborn female rats (1–2 h), that PGE2 changes neuron morphology by increasing the number and density of dendritic spines. Using in vivo experiments, they reported the expression of PGE2 receptors EP1, EP2 and EP3 genes in the POA of PN0 female rat. In the same study, it was demonstrated that PGE2 is a mediator of E2 signal for the induction of the Spinophilin protein production, a marker of dendritic spines. Finally, Amateau and McCarthy (2002) have also identified the POA as a sexual dimorphic structure since they observed a greater Spinophilin protein quantity (two and half more) in newborn males than in newborn females (Amateau and McCarthy, 2002). Two years later, the same team has demonstrated that PGE2 is directly implicated in the male sexualization of the developing POA and induced sex behavior in adult male rat. They also showed that E2 regulates the synthesis of PGE2 by upregulating PTGS2 expression and COX-2 enzyme production in the POA of 3 days old rat (Amateau and McCarthy, 2004). The cerebellum is an area located in the rostral roof of the 4th ventricle and functionally associated with emotional control, motor, cognitive, and social behaviors (Adamaszek et al., 2017; Voogd and Glickstein, 1998). In 2012, Dean et al. brought the demonstration for the pivotal role of PGE2 in the development and functional acquisition of the cerebellum. In this study it was reported that PGE2 regulates the dendritic spines of Purkinje cells and cerebellum volume between PN7 and PN13 in male and female rats. This involvement of PGE2 in the differentiation of the cerebellum in this short window is directly associated with adult behavior induction like play, sensory threshold and object exploration (Dean et al., 2012). These studies indisputably show a key role of PGE2 in the differentiation of POA and of the cerebellum and therefore of the brain at an early postnatal stage. NSAID-inhibition of PGE2 during brain development could have disruptive effects and could be a real concern.

Very few studies were published on the toxicological effects of NSAIDs at environmental doses. Exposing common carps with NSAIDs-manufacturing plant effluent causes genotoxicity and apoptosis in blood cells (SanJuan-Reyes et al., 2015). Other studies show, after environmental NSAIDS exposure, an induction of oxidative stress in fish, crustaceans and bivalves (Gonzalez-Rey and Bebianno, 2014; Novoa--Luna et al., 2016; SanJuan-Reyes et al., 2015). Teratogenicity experiments using Xenopus embryos indicate that diclofenac at environmental doses causes malformation of several organs with acephaly, cephalic edema and a diminution of axial length (Chae et al., 2015). No studies reporting NSAIDs effects on neurotoxicity in mammals are available, nevertheless inhibiting COX-1 and COX-2 enzymes and so preventing PGE2 production has a negative impact on brain development. In vitro incubation of POA neurons with indomethacin prevents dendritic spines formation and spinophilin production induced by PGE2 (Amateau and McCarthy, 2002). Administration of indomethacin in newborn rats (6 hrs of birth) blocks the production of spinophilin and decreases the density of dendritic spines in POA male rats (Amateau and McCarthy, 2002, 2004). This structural modification of POA impacts the behaviors it controls. Indeed, exposure of neonate rats (between PN0 and PN1) to NSAID disturbs sexual behavior in adult males, not in adult females. Thereby a neonatal indomethacin treatment induces an decrease of sexual adult male behavior with an increasing of latency to mount, intromission, a decreasing of mounts and intromissions frequency and a cancellation of ejaculation (Amateau and McCarthy, 2004). Non-neuronal cells of the POA are also sensitive to NSAIDs since POA microglial cells are more numerous and ameboid in male than female in neonate rats. This sexual dimorphism, dependent of PGE2, is abolished with indomethacin treatment inducing a loss of masculinization of the POA (Lenz et al., 2013). Curiously the inhibition of COX-1 and COX-2 enzymes in the cerebellum has an opposite effect on neuron morphology but still impacts adult behavior. Treating neonate rats with NSAIDs (indomethacin and paracetamol) between PN7 and PN13 induces an increase of dendritic spine length of Purkinje cells only in male PN14 cerebellum and a modification of behaviors associated to this cerebral structure. Male adult rats exposed to NSAIDs in neonatal stage present a reduction of play behavior and the sensory threshold and an increase of object exploration time (Dean et al., 2012). NSAIDs doses used in these studies are pharmaceutical and greatly extra-environmental, but a chronic NSAID developmental exposure with environmental doses and especially in the precocious postnatal window could have a real impact and remains largely underexplored.

5. When drugs become environmental pollutants: what about epigenetics consequences?

Recently, it became evident that epigenetics prior to or around the birth can profoundly modify brain development and can be linked to various neurodevelopmental syndromes (reviewed by Lo and Zhou,

2014). Epigenetics disorders fit well with the time lag often observed for such syndromes, which may appear many years after exposure or in offspring. Although less is known about epigenetic consequences of in utero and perinatal chronic exposures to environmental pollutants, data presented in the current review ask questions about the putative role of epigenetics input, especially in behavioral changes observed between childhood and adulthood, or for the brain sexualization. For instance, in human, maternal exposure to environmental heavy metals during pregnancy is associated with differential DNA methylation in new-borns, especially on genes involved in neurogenesis (Zeng et al., 2019).

This question is made relevant by the outcome of works establishing a causal link between a well-known endocrine disrupting compound, the Bisphenol A (BPA), and its epigenetic consequences. In mouse, BPA exposure modifies the expression of several genes involved in brain development by altering the genomic imprinting at various genetic loci. This effect is transmitted across generations. In addition, BPA has been suggested to affect the DNA methylation status, as well as histones post-translational modifications after in utero exposure (reviewed by Santoro et al., 2019). Similar effects are suspected about other pollutants, such as Permethrin (Bordoni et al., 2019), for which low dosage exposures during neonatal brain development led to significant reduction of H3K9me3 marks at Th and Nurr1 promoter regions, both genes being related to the dopamine-synthesis pathway. Although these pollutants are outside the scope of our review, they clearly illustrate the potential epigenetic impact of pollutants. What's about drugs when they are pollutants? Even if no studies are available at this level (epigenetics aftermath of drugs detected in the environment), data are now known on the epigenetic effect of drugs when administered during pregnancy or gestation, or around the perinatal period.

5.1. Antibiotics

In addition to the overall effects of antibiotics on the nervous system (described above), various studies concerning the epigenetics alterations mediated by antibiotics have been published. It was demonstrated that zebrafishes are sensitive to a common biocide (Triclosan), when administrated to 8-cells developing larvae at low doses (50 or 100 μg/L), until hatching. This treatment modifies DNA methylation in a locus-specific manner (mainly within introns and intergenic sequences), while global DNA methylation is not affected. Consequently, the expression of few genes is modified. Interestingly, in zebrafish, antibiotics trigger mechanisms of acclimation leading to an increase resistance of organisms. Here, DNA methylations are likely to precede the adaptive response (Falisse et al., 2018).

Recently, a special attention was paid to how the composition of gut microbiota may contribute to establish epigenetic changes, leading to modulation of lifelong health and diseases, via the gut-brain axis. In humans, the role of maternal and neonatal nutrition, as well as microbiota composition has been reviewed by Indrio et al. (2017). The period during which epigenetic imprinting is the most active is referred as the 1000 days period (from conception to the second anniversary). During this period the microbial colonization takes place first in utero, then after birth. Because the microbiota-related epigenetic regulation of gene expression could take place in various brain regions, the impact of the "quality" of the maternal microbiota has been suspected of importance in preventing or promoting brain development disorders (Indrio et al., 2017). Evidence accumulate that a disturbed microbiota is related to various neurodegenerative diseases (Quigley, 2017). In fact, gut microbiota is now looked as an important epigenetic regulator since some of their metabolites (as SCFAs) act as HDAC inhibitors, and play a role through DNA methylation, post-transcriptional histone modification, and chromatin restructuring, all together resulting in altering genes expression (Kaur et al., 2021). By the way, pharmacological factors (such antibiotics) that modify microbiota can be related to the development of chronic diseases. In human, the predominant gut microbiota of pregnant women was associated to the postpartum methylation profile of their blood DNA and correlated with differential methylation status of gene promoters linked to cardiovascular diseases (Kumar et al., 2014).

Even if there is no direct evidence between epigenetics, antibiotics in the environment and neurodegenerative diseases, all the ingredients are there to consider a possible impact, including via pathways other than the microbiota.

5.2. Antidepressants

Literature related to human risk constituted by antidepressants exposure at environmental doses during pre- and peri-natal development is poorly documented, but epigenetic consequences of maternal treatment during pre- and perinatal development are more documented (in animal models or in human clinical studies). Since fluoxetine is commonly prescribed for the treatment of depression in pregnancy, its impacts on in utero exposed children has been questioned, including at the epigenetics level. Alteration of DNA methylation levels has been detected in the hippocampus of rats that were exposed to fluoxetine during their development (Silva et al., 2018). This alteration correlates with modifications of the anxiety-related (social) behavior at adulthood, as result of an acquired imprinting. These studies converged with the findings of Boulle et al. (2016), which demonstrate that fluoxetine modifies the epigenetic regulation of the hippocampal brain-derived neurotrophic factor (BDNF) coding gene, in the offspring of treated female. It was actually found that developmentally administered fluoxetine increases H3K27me3 levels at the BDNF promoter, in accordance with the decreased expression of BDNF mRNA in the hippocampus of offspring. More, these modifications were associated to increased depressive-related behaviors in adult female offspring, suggesting a long-term effect of fluoxetine treatment during gestation and/or lactation. Epigenetic effects of developmental exposure to fluoxetine were also suggested by studies on zebrafish (Boulle et al., 2016). In addition, a 6-day exposure to fluoxetine at a fetus-relevant concentration inhibits cortisol secretion at adulthood in developmentally exposed zebrafish, and this alteration is persistent for three generations of unexposed progeny, as well as alterations in exploratory behaviors in males (Vera-Chang et al., 2018). Transcriptomic analysis of kidneys cells showed that fluoxetine exposure modified signaling pathways implicated in cortisol production on animals of the three generations. Neural effects are suspected to be involved through the HPA axis control (Vera-Chang et al., 2018).

In human, the involvement of epigenetic mis-regulations is suggested through in vitro and in silico approaches using differentiated human neuroblastoma cells treated with a mixture of psychoactive pharmaceuticals including fluoxetine at environmentally relevant concentrations. A recent study identified alterations in neuronal gene sets expression associated with neurological disorders such as Autism Spectrum Disorders (ASD), Alzheimer's disease and schizophrenia. Among the genes exhibiting expression alterations, several genes coding synaptic proteins associated with ASD were affected (Kaushik et al., 2017).

5.3. Non-steroid anti-inflammatory drugs (NSAIDS)

Here again, no studies are available to prove a direct correlation between NSAIDS (as pollutants) and epigenetics alteration of brain development. But there is straight evidence of (i) epigenetic changes due to NSAIDS, (ii) the epigenetic control of brain feminization and (iii) the epigenetic control of PGE2 biosynthesis via an induced COX2 expression. In this context, it is tempting to propose that chronic exposure to NSAIDs may alter sexual behavior also through epigenetic mechanisms.

Epigenetic changes due to NSAIDS have been studied in patients having various cancers. Clinical trials and ex-vivo analyses both suggest that aspirin and other NSAIDS induced changes in promoters'

methylation, thus leading to gene silencing. This effect has been attributed to DNMT1 inhibition (reviewed by Yiannakopoulou, 2014). In animal studies, this local effect was found associated to an overall effect. Indeed, NSAIDS reverse global DNA hypomethylation in colon cancer rat-models. Finally, the fact that aspirin is known to acetylate proteins leads to assay whether it also acetylates histones, among other cellular proteins. This is actually the case, but it remains to establish whether this direct post-translational modification impairs gene expression (Bhat, 2011). More recently, it has been found that Ibuprofen and Ibuprofen-CoA causes dose-dependent inhibition of histone acetylation, especially H2B K12/K15Ac and H3 K56Ac, in cultured cells (Shrimp et al., 2018).

Because epigenetics is involved in various endogenous and exogenous pathways to exert long-term control over gene expression, it was tempting to verify its role in estradiol-mediated brain masculinization, an effect herein described (see previous paragraph). Doing so, it was demonstrated that estradiol suppresses DNMT activity, leading to an overall DNA demethylation in male developing POA. This study confirms that feminization is an active repression of masculinization process, reinforced by epigenetics imprints (Nugent et al., 2015).

Finally, the epigenetic activation of the COX2 promoter by p300, a histone acetyl transferase, has been confirmed in activated monocytes, leading to PGE2 production (Liu et al., 2020). As mentioned before, increased COX2 expression and PGE2 production within dendritic spines leads to the hypothesis that COX2 is an active modulator of neuronal plasticity, involved in sex differentiation (Amateau and McCarthy, 2002). The fact that COX2 activation appears finely and strictly controlled at the spatial level speaks up for an epigenetic control in neurons, as previously demonstrated in monocytes.

In conclusion, albeit no direct evidence about epigenetic consequences of in utero and/or perinatal chronic exposures to drugs as environmental pollutants still exists, converging evidence suggests a possible impact. It therefore appears important not to overlook epigenetics effects when addressing this issue. Further studies remain to be done, especially in humans. The central issue being the dose at which these effects could be significant.

6. Non-invasive neuroimaging to advance knowledge on EDCs?

Evidence from epidemiological and experimental data of the close relationship between environmental contaminants and adverse functional and metabolic effects are mounting. Nevertheless, to date, there are very few dedicated non-invasive and translational methods with the ability to measure, demonstrate and validate a direct and specific link between the alteration of the function of the endocrine system and Endocrine disruptor compounds (EDCs) in-vivo in the brain. Methodologies and models are lacking for evaluating the mechanisms and pathways underlying the effects of EDCs and their development into diseases. Here, the potential of magnetic resonance (MR) techniques to assess risk factors induced by potential EDCs is introduced. In this paragraph, we aim to show in a non-exhaustive manner that non-invasive neuroimaging methods can be adapted to further advance and fasten knowledge on EDCs.

6.1. Magnetic resonance imaging and spectroscopy (MRI and MRS) (Haacke et al., 1999)

That Nuclear Magnetic Resonance (NMR) techniques are powerful for the investigation of the structure, function and metabolism of the brain both in animal models and human is not to demonstrate anymore. MR imaging (MRI) is well known for its non-invasiveness, its important contrast between soft tissues and its high spatial resolution compared to other macro-imaging techniques (X rays, Positron Emission Tomography, Ultrasound). In addition, crucial technological developments have been carried out during the past 20 years and the advent of high magnetic field strength horizontal superconducting magnets (up to 11.7 T in humans, up to 21 T in rodents) coupled to improved hardware enabled an unprecedented increase of the sensitivity (Hespel and Cole, 2018; Wald, 2019), the spatial and temporal resolutions and the development of novel molecular applications (Chemical Enhanced Saturation Transfer (CEST, PARACEST (De Leon-Rodriguez et al., 2009; Soesbe et al., 2013), Hyperpolarisation techniques …). Despite all these assets, MR techniques lack sensitivity. Thus, molecular imaging possibilities are limited with extremely low compound concentrations (below millimolar). This poor sensitivity may explain the lack of interest for MR investigations on potential EDCs, which can be present in brain structures as traces only and which presence can rarely be measured and quantified with MRI or MR Spectroscopy (MRS) techniques. Interestingly, the MR literature represents an abundant source of knowledge on the potential effects of EDCs and their mechanisms since many studies investigated the dose-effect of various pharmaceuticals albeit not at the very low concentrations encountered in the environment.

6.2. MR biomarkers could benefit knowledge on the endocrine effects of compounds

MRI facilitates the in-vivo diagnosis, prognosis and therapeutic monitoring of various brain diseases such as cancer, neurodegenerative diseases and neuropsychiatric diseases (Alzheimer, Parkinson, dementia, epilepsy, multiple sclerosis …). Studies can be performed relatively fast, and longitudinally with little discomfort for patients. Therefore, assessment of repeatability and reproducibility of the outcome can be performed with increased accuracy. MR can also detect various conditions such as stroke and traumatic brain injury, hemorrhage, inflammation and edema.

Endocrine disruption also involves metabolic alterations resulting in obesity, diabetes and liver diseases that remain to be understood … Multinuclear applications of MRS and chemical shift imaging (CSI) can be useful for investigating neurometabolic disorders. Moreover, metabolic changes can reveal the very early stages of disease prior to lesion detection (Lei et al., 2009). This is important since EDCs' effects may develop over years and even decades or have consequences in adulthood only.

Also, MR investigations demonstrated their usefulness upon assessment of the effects of various compounds (Cherix et al., 2020; Kluza et al., 2011; Padhani and Leach, 2005; Wassmuth et al., 2001) both in humans and in animal models. The dose-responses of a variety of MR contrast agents such as gadolinium (Gd)-based contrast agents (Prybylski et al., 2019; Robert et al., 2020; Woodard et al., 2012) or iron oxide nanoparticles, were largely assessed (Diana et al., 2013; Kim et al., 2013). Many other MR studies also investigated the effects of antidepressants (Cherix et al., 2020), antibiotics or analgesics (Bar-Or et al., 2018; Jantzie et al., 2020). MR techniques (Diffusion, Perfusion, blood oxygen level-dependent (BOLD) functional MRI …) can be used to assess the dose-impact of these compounds using surrogate markers of various parameters (permeability, vessel radius, water diffusion, blood volume, blood flow …) that can be mapped on a voxel-by-voxel basis thereby also displaying the heterogeneity and extent of the effects. Moreover, the impact of a defined compound on the behavior or alterations of this behavior can also be investigated with functional MR techniques.

6.3. Investigating the effects of antidepressants and NSAIDs with MR techniques

With advanced technological developments in MRI across the past 20 years, BOLD-fMRI and resting-state-(RS)-fMRI became the methodologies of choice for investigating neuropsychiatric disorders. Task-based fMRI has identified altered functional activity in a wide spectrum of psychiatric disorders while RS-fMRI is recognized as a predictor of treatment response in major depressive disorder (MDD), schizophrenia, anxiety disorders and autism where brain connectivity is often altered. fMRI was also extensively used for a better understanding of pain and

analgesia-related phenomena (Borsook and Becerra, 2006). There has recently been increased use of RS- fMRI in the context of studies addressing brain network dynamics involved in response to antidepressant and analgesics treatments, both in terms of predicting response to treatment as well as understanding changes in functional brain connectivity after effective treatments. Dichter et al. (2014) reviewed the linkages between RS-fMRI and treatment response in MDD thereby identifying specific biomarkers and specific patterns of brain network dynamics affected by antidepressants. A variety of antidepressant substances that have been increasingly examined with these MR techniques demonstrated to have toxic effects on the reproductive system and hormones (Dichter et al., 2015). This is the case of ketamine, which recently attracted a large interest for its impact on metabolism (Bednarik et al., 2021; Qi et al., 2017). Fluoxetine and norfluoxetine were also abundantly studied with MRI and MRS and are well-known EDCs present in aquatic systems (Mennigen et al., 2011). Moreover, several agents used to correct the endocrine imbalance were also employed as antidepressants such as melatonin and glucocorticoids (Antonioli et al., 2012). Numerous effects of these agents was examined and identified (Kalafatakis et al., 2018). In particular, glucocorticoid receptors are recognized as important targets for EDCs. Of note, important knowledge on the underlying effects of these agents and their potential markers examined with MR techniques was accumulated. An important database exists therefore allowing the identification of risk factors linked to EDCs. In addition, important cohorts of responder and non-responder patients followed over years could serve to examine the long-term effects of a variety of compounds and their mixture. Their physiological and endocrine status is already often followed across years.

Neuroimaging techniques have also a considerable role to play in the more appropriate development of analgesics. Most of them only have a significant effect on a minority of patients. Despite the promise of interesting signs of progress, the use of mild analgesics such as paracetamol, ibuprofen and aspirin in the general public and pregnant women increases and is generally perceived to be safe (Thiele et al., 2013). Unfortunately, they also have potent disrupting effects on hormonal homeostasis, leading to congenital malformation in both animals and humans through anti-androgenic mechanisms (Kristensen et al., 2011, 2018). Neuroimaging techniques are usually effective at discriminating responsive and non-responsive patients and reveal novel targets, which could be of value for a better understanding of the endocrine mode of action of these compounds.

6.4. Metabolism and EDCs

EDCs interfere with the endocrine system by altering mechanisms linked to hormone secretion or elimination. EDCs can also mimic hormone action. All these modes of action can disrupt the regulation of general homeostasis of the body and contribute to adverse metabolic phenotypes. EDCs can also predispose patients to several metabolic syndromes and alter nutrient ingestion and metabolism. Moreover, specific individuals may be more affected than others such as the developing fetus, which is more sensitive to endocrine perturbations. Fetus exposure to EDCs may cause irreversible effects that may become detectable later in life. In this context, MRS can be useful. An example was given by Kunz et al. (2011) who used proton MRS at 9.4 T to assess the effect of perinatal exposure to bisphenol A (BPA) on cerebral structural development and metabolism after birth in rat pups. On postnatal day 20, in vivo metabolite concentrations in the rat pup hippocampus were measured. Exposure to low dose BPA during gestation and lactation resulted in subtle and regional neuronal and glial alterations in brain development in offspring. Furthermore, BPA exposure led to significant changes in the Glutamate to Aspartate ratio in the hippocampus, which is postulated to reflect impaired mitochondrial function and probably implicates a reduced ability of the brain to oxidize glucose especially in conditions of elevated energetic demand (Kunz et al., 2011). The changes observed after prenatal BPA exposure will likely imply long-lasting effects on cognitive development and function. While such studies are needed and somehow not difficult to realize, investigations of EDCs effects in huge cohorts of humans may benefit the assessment of the levels of exposure to EDCs. Such screening studies can be performed with NMR metabolomics and were proposed by the EDCMET project (Küblbeck et al., 2020). Using serum NMR platforms, NMR spectroscopy can simultaneously quantify 230 metabolic features such as serum proteins, lipids, fatty acids, glycolysis substrates, amino acids, ketone bodies and many other molecules to obtain signature metabolic profiles affected by EDCs.

Although few MR studies have been conducted yet in the context of pharmaceutical EDCs, the specific case of MR contrast agents can illustrate the potential of MRI and MRS for the detection and evaluation of endocrine disruption.

Gd is a heavy metal of the lanthanide group. Chelated forms of Gd are used in MRI and MR angiography to avoid the toxicity of Gd^{3+}. Recently, tissue deposition of Gd was demonstrated in various rodent and human tissues of the body (Sato et al., 2013; Wáng et al., 2015) and of the brain (Gulani et al., 2017). Free Gd^{3+} ions induced cell death, oxidative stress and accumulation of reactive oxygen species (ROS) in rat cortical neurons (Feng et al., 2011). Briner et al. (2000) reported important behavioral responses of mice exposed to lanthanides with consequences on their development further confirmed by Feng et al. (2006) who also showed altered DNA and protein/DNA concentrations in the brain. Interestingly, the current literature does not report longitudinal BOLD-fMRI or perfusion studies in animal models or humans combined with behavioral assessments following Gd injections although 30 million doses are consumed each year (Guo et al., 2018). Non-invasive functional evaluations could be insightful as predictive factors of parkinsonism since Gd deposition in the dentate nucleus and the globus pallidus induced symptoms (Welk et al., 2016) but require long-term follow up. In the context of EDCs, cell cultures demonstrated that toxic effects on thyroid hormones depended on the chemical structure and dose of Gd- based contrast agents (Ariyani et al., 2016) but no in-vivo study has been conducted to date. Again, as described earlier for other pharmaceuticals, Gd-based contrast agents are difficult to remove with the usual sewage treatment technology. Amounts of Gd-based contrast agents in wastewater significantly increased with the increasing use of MRI technology (Brünjes and Hofmann, 2020; Inoue et al., 2020) emphasizing the need to change medical practices.

More recently, manganese ions (Mn^{2+}) attracted overwhelming interest owing to their paramagnetic properties enabling them to be used as contrast agents and to depict the rodent brain cytoarchitecture with unprecedented dose-dependent MR contrast. A better understanding of their toxicity was also obtained using MRS (Just et al., 2011; Just and Gruetter, 2011). Mn-induced neurotoxicity is well known with reference to occupational Mn exposure. Due to the risk exposure of smelters and welders, it was shown that Mn-exposure disrupted the endocrine systems of Mn-exposed workers (Long et al., 2014). Mn uptake was reported in various human brain structures (caudate nucleus, substantia nigra, pituitary gland, ventromedial hypothalamus …). A wealth of human studies demonstrated that significant hyperintensities in T1-weighted MR images of Mn-exposed workers occur (Criswell et al., 2019). Various MR methodologies can be used to identify Mn toxicity: the pallidal index (PI) can be used to quantify hyperintensities due to increased Mn^{2+} concentrations but relaxometry may also quantify Mn content while proton MRS can be useful in detecting the impact of Mn on metabolites (Just et al., 2011). Notably, metabolites can be markers of Mn-induced Parkinson or encephalopathic symptoms (Peres et al., 2016).

Many other metal compounds play a role as EDCs (reviewed in Iavicoli et al. (2009)). MRI/MRS can identify the influence of these metals on the endocrine system by exploring their mechanisms of action, their content or their effects on behavior. Iavicoli et al. (2009) also pointed at the lack of studies on the effects of mixtures of these metals. Some of them such as Zinc (Zn) or Europium (Eu) or copper (Cu), iron

(Fe3+) can also be used in the chemical structure of contrast agents. In an identical manner to Gd-based compounds, metal compounds used in the medical practice find their way to rivers, where they may have deleterious effects on invertebrates and vertebrates (Iavicoli et al., 2009).

In conclusion, the in-vivo detection of EDCs' amounts and an improved understanding of their mechanisms and modes of action are much needed to validate the associated risks factors and determine appropriate predictive markers. But this is challenging. Magnetic Resonance techniques can represent a major tool in this context with long-term accumulated data and already developed methodologies that just need to be used.

7. Discussion

7.1. Are pharmaceutical drugs endocrine disruptor compounds?

The pharmaceutical drugs considered in this article (antibiotics, antidepressants, anti-inflammatories) induce neural effects. Whether all these neural effects occur through an endocrine disrupting mode of action still needs to be thoroughly documented, in particular at doses close to the environmental exposure. There are, however, several evidences highlighted in this article that suggest that these substances may act as endocrine disruptors.

For antibiotics, the evidences in favor of an endocrine disrupting mode of action are provided by the studies performed in aquatic models and using low environmentally relevant doses of these substances. In fish, exposure to these molecules impaired reproduction probably through modifications of the gonadotropic axis and steroidogenesis (Kim et al., 2012, 2017). The thyroid axis was also targeted leading to affected growth and development (Yu et al., 2020). In mammals, such studies are still lacking. In particular, whether the effects induced by exposure to antibiotics on social and mood behaviors in children (Slykerman et al., 2017) and animal models (Degroote et al., 2016; Leclercq et al., 2017; Tochitani et al., 2016) involve a disruption of neuroendocrine systems needs further investigation. It is, however, important to keep in mind that these behaviors are known to be regulated by sexual and thyroid hormones.

The SSRIs antidepressants such as fluoxetine or sertraline, the most commonly prescribed ones, showed to affect social, anxiety-related and reproductive behaviors in aquatic species after developmental exposure to doses compatible with environmental contamination (Sehonova et al., 2018). Such alterations suggest endocrine disruption effects triggering the hypothalamic-pituitary-adrenal and gonadotropic axis (Mennigen et al., 2011). For human assessment of the risk associated with developmental antidepressant exposure, the literature deals with developmental exposure to SSRIs at pharmacological doses, in the context of maternal treatment for major depressive disorder during pregnancy and/or postpartum depression. Studies in rodents report long-lasting endocrine and behavioral alterations on the developmentally exposed offspring, and neural alterations are described, susceptible to be responsible for these long-term effects. In the study of Soiza-Reilly et al. (2019), it was shown that all the inhibitors tested exerted endocrine disrupting effects, with different mechanisms from one molecule to another. Therefore, potential effects of SSRIs as endocrine disruptors at environmental doses have to be investigated on mammal models.

The NSAIDs interfere with the E2 dependant mechanisms during brain development. One of the numerous actions of E2 signal is to activate COX-1 and COX-2 enzymes for the conversion of Arachidonic Acid to PGE2 (Hermenegildo et al., 2006). PGE2 have a key role in the brain sexualization by regulating the male differentiation of the preoptic area and cerebellum (Amateau and McCarthy, 2002, 2004). So, the inhibition by NSAIDs of COX enzymes and consequently of PGE2 production during CNS development results in a reduction of sexual behavior, play behavior, and of the sensory threshold as well as an increase of object exploration time in adult male (Amateau and McCarthy, 2004; Dean et al., 2012). At the cellular level, NSAIDs impact the morphology of neuronal and microglial cells by inhibiting spinophilin production, a protein specific to dendritic spines (Amateau and McCarthy, 2002, 2004; Lenz et al., 2013). Since microglia produce prostaglandins, express prostaglandin receptors, and are activated during the critical period for sexual differentiation, some authors have hypothesized a role of microglia in E2-induced PGE2 production in the POA (Welberg, 2013). Microglial PGE2 has been shown to play an important role in the proliferation of astrocytes, identifying PGE2 as a key neuro-inflammatory molecule that triggers the pathological response related to the uncontrollable proliferation of astrocytes (Zhang et al., 2009). These results are important to elucidate the role of activated microglia and PGE2 in astrocyte proliferation and to suggest a potential disturbance in chronic exposure to anti-inflammatory agent molecules.

Even if reported studies in this review have used pharmacological doses, whether antibiotics, antidepressants and anti-inflammatories induce adverse effects on the central nervous system development at environmental exposure remains to be answered.

7.2. Pharmaceutical drug exposure and susceptibility to neurodegenerative disease, what about epigenetic?

The epigenome is responsible for the functional use and stability of information within the genome, but in contrast to the stable genetic material, the epigenome fluctuates in response to environmental exposures. Pharmaco-epigenetics is an emerging aspect of the usual pharmaco-vigilance. It concerns alterations in gene expression of drug-metabolizing enzymes and transporters that result in interindividual variations in drug responses. During the developmental period from newborn to childhood, inter-individual variations are combined with changes related to the differentiation and growth of tissues and organs. All are under epigenetic control, and therefore sensitive to epigenetic deregulations. As previously mentioned, about nothing is known about relationships between epigenetic and pharmaceutical pollutants (i.e. low-doses and long exposures). However, there is growing evidence suggesting such relationships. (1) Brain development and neurodegenerative diseases are under epigenetic control. Indeed, individuals with neuropsychiatric and neuro-degenerative diseases display epigenetic brain programming disturbances (Abdolmaleky et al., 2008). Studies of monozygotic twins discordant for schizophrenia and bipolar disorders reveal a significant difference in DNA hypomethylation of gene networks and pathways directly relevant to psychiatric disorders and neurodevelopment. Analyses of post-mortem brain tissues reveal DNA hypomethylation in psychosis patients (when compared to controls), for the same DNA regions than those identified in twins (Dempster et al., 2011). Brain masculinization is a consequence of testosterone production which epigenetically regulates sex differences in the neuronal structure of some hypothalamus nuclei (McCarthy et al., 2009). (2) Pharmaceutical drug exposure alters epigenetic pathways of brain development. Indeed, in utero exposure to many substances results in neuronal injury related to epigenetic changes and results in long-term neuro-developmental impairment in the offspring. More, transgenerational epigenetics may also explain the fact that developmental abnormalities, impairment in learning and memory, and attention deficit can occur even in the absence of direct fetal exposure, when drugs are used prior to conception (Neri et al., 2015). (3) The consequences of intrauterine exposure to drugs can appear very late, at adolescence or adulthood. As an example, prenatal exposure to xenobiotics probably leads to alteration of the hypothalamic-pituitary-adrenal (HPA) axis. These alterations are believed to increase the susceptibility to adult neuropsychiatric disorders (such as depression and schizophrenia). Among the possible mechanisms of action, xenobiotics can directly induce epigenetic alterations, modifying the expression of main fetal genes (such as hippocampal glucocorticoid receptor, adrenal steroidogenic acute regulatory protein …) (Zhang et al., 2014).

To conclude, it appears essential to keep in mind that epigenetic deregulations are a powerful way to account for time-lagged and even transgenerational effects, often observed in neurodegenerative pathologies and could be crucial to validate the involvement of environmental pollutants at their onset (during childhood or later in life).

7.3. Alternative methods for the assessment of the impact of endocrine disruptor compounds on the central nervous system

A large set of MR-based data and know-how has been accumulated across years to evaluate brain dose-responses to various pharmaceuticals. This knowledge could be advantageous to evaluate in-vivo the impact of various molecules acting as EDCs. Long-term follow-up of changes in behavior, neuroanatomy, function and metabolism of EDC-exposed populations could be envisaged and associated with various measurements in drinking water or sewage. Moreover, important databases of the effects of antidepressants, antibiotics and NSAIDS on brain function and metabolism exist and could be helpful for modelling purposes. Although novel methods exist, one important disadvantage of MR techniques is their low sensitivity, which does not permit the detection of traces or very low doses of pharmaceuticals, impeding reliable and direct attribution of longitudinal changes to specific molecules considered as EDCs. Nevertheless, MR can be efficiently coupled to other imaging modalities such as ultrasound, CT or PET, which have molecular imaging possibilities. Nowadays, PET-MRI is a well-accepted technique both in rodents and humans allowing the coupling of the molecular potential of PET to the high spatial resolution of MRI (Musafargani et al., 2018) with little-invasiveness and could be effective at EDC detection at very low doses. While in vivo analysis is of paramount importance, the use of MR microscopy and MR spectroscopy to evaluate ex-vivo and in-vitro specimens is not to be neglected. In this regard, one can think of the systematic and longitudinal analysis of water samples with high-resolution MR techniques (HR MAS) (Lucas-Torres and Wong, 2019), which could reveal the presence of various substances and can be coupled to mass-spectroscopy techniques (Emwas, 2015).

8. Conclusion

Scientific literature reported in this review shows real adverse effects of pharmaceutical products present in the environment on the development of the central nervous system. The risk for future generations could be a concern and has to be evaluated. Indeed, food and water for human consumption are contaminated and the exposure to these pharmaceutical substances occurs during the adult life but also at earlier stages including foetal development. The chronic exposure to these drugs even at environmental doses for human but also farm animals and wild life is, at this time, largely underestimated. Metrology studies have to be multiplied to measure these pharmaceuticals in the whole environment (macro and microenvironment) to define our exposome and evaluate the risk of this environmental exposure. The question of the implication of the microbiota is emerging, futures studies have to precise if these drugs exert their adverse effects on the CNS development by disrupting the gut-brain axis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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