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Neuroactive steroids as targets of micro- and nano-plastics: Putative impact on brain function and disease

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ABSTRACT

Among environmental pollutants, microplastics (MPs) and nanoplastics (NPs) represent a major threat to marine and terrestrial ecosystems because of their widespread distribution, environmental persistence, accumulation in animal and human organs, and toxicity. MPs and NPs target the major endocrine components, including the hypothalamic-pituitary-adrenal (HPA) and gonadal (HPG) axes, thus affecting steroid milieu with repercussions for peripheral endocrine glands and brain functions. Steroid hormones, either locally synthesized by neurons and glial cells, or reaching the brain from peripheral glands, exert neuroactive actions regulating neuronal excitability, neurogenesis, mood, and behavior. Despite numerous studies investigating the endocrine-disrupting effects of MPs/NPs and their potential reproductive toxicity, the implications of such effects on brain neuroactive steroids are poorly investigated. Here, we first illustrate how neuroactive steroids affect brain functions, then we review clinical and preclinical studies assessing the effects of MPs/NPs on neuroactive steroid levels, with the aim to understand putative implications for mental health.

1. Introduction

The massive expansion of plastic manufacturing has dramatically increased the environmental impact of microplastics (MPs, size <5 mm) that are abundant into ecosystems worldwide, posing a considerable hazard for environmental and biological well-being. Compared to MPs, the lower size of nanoplastics (NPs, size ≤1 μm) implies different ecological transport and adsorption, timing of additives release and faster absorption by animals and pathways into the food chain, which render them potentially more ecologically detrimental (Amobonye et al., 2021). Since 1997, after the discovery of the so-called "Great Pacific Garbage Patch", i.e., the largest accumulation of plastic waste in the ocean, four additional big plastic islands have been identified in the oceans (coincident with the main ocean vortices, two in the Pacific, two in the Atlantic, one in the Indian ocean), but smaller and more dispersed plastic islands are also present in the Mediterranean and the Caribbean seas, with new plastic forms (i.e., plasticoncrete, plastimetal and plastisessiles) discovered not only in the Mediterranean sea (Mallorca island) but also in the North sea (Helgoland island) and in the sea of Japan (Hikoshima island), confirming that they are not local phenomena (Ellrich et al., 2023). Single-use plastic products are everywhere, and many are integral parts of our daily lives, including personal care products, clothes and detergents. Products containing synthetic polymers such as polyethylene terephthalate (PET, e.g., water bottles), polypropylene (PP, e.g., bottle caps, face masks), polystyrene (PS, e.g., cutlery), expanded polystyrene (EPS, e.g., protective packaging, hot drink cups) have long-lasting and non-degradable characteristics and, as such, dramatically impact on the environment and living organisms. Consequently, MPs and NPs are now ubiquitous in our natural environment, including fish, meat and vegetables that we eat daily, and in drinking water, representing an invisible threat to animals and human health.

The possibility that such a massive presence of MPs and NPs in the living environment could represent a serious risk to our health has stimulated an intense clinical and preclinical research activity, which reported the presence of MPs/NPs in almost every organ and site of the human body, including lung, liver, spleen, kidney, intestine, blood, saliva, hair, bronchoalveolar fluid, breast milk, placenta (Thompson

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et al., 2024). Recently, their presence in the human brain has also been confirmed (Nihart et al., 2025), posing a serious health threat for neurological and neuropsychiatric disorders.

Among the targets for MPs/NPs, the endocrine system has been widely investigated. According to a recent European Commission report (2023), being compounds that "*under certain conditions can impact on the hormonal system of humans and animals*", MPs and NPs are considered as possible endocrine disruptors and, hence, should be carefully evaluated for their potential impact on human and animal health. To their endocrine-disrupting effects contributes the fact that MPs and NPs absorb and transport harmful chemicals commonly used as additives in plastic production (e.g., bisphenols, phthalates, perfluorinated compounds, dioxins, polybrominated diphenyl ethers, polychlorinated biphenyl, polycyclic aromatic hydrocarbons, organic contaminants, flame retardants), some of which share structural similarities with endogenous hormones and may thus interfere with the physiology of the endocrine glands (Yilmaz et al., 2020).

Here we review the effects of MPs/NPs on steroid hormone levels across different species, focusing on exposure to selected types of MPs/NPs rather than on the endocrine-disrupting effects of MPs/NPs additives, which have been recently reviewed elsewhere (Li et al., 2024a; Yilmaz et al., 2020).

2. Neuroactive steroids

Within the endocrine system, steroid hormones act as chemical messengers to control homeostasis, and to regulate several functions, including cell metabolism, stress, immunity, development, reproduction (McEwen, 2020). Steroid hormones are synthesized not only peripherally from adrenals and gonads (i.e., their major sources), but also directly from the brain, where they act through a fast non-genomic action via ligand-gated neurotransmitter receptors or membrane-bound steroid receptors, to regulate neuronal excitability, neurodevelopment, sexual dimorphism, neurogenesis, neuroimmune function, mood, and behavior. Steroid hormones, locally synthesized by neurons and glial cells, were termed "neurosteroids" (Baulieu, 1998); however, given that all steroid hormones can affect brain function (independently from their origin), we will refer to them as "neuroactive steroids" (Paul and Purdy, 1992).

Despite the numerous studies investigating the endocrine disrupting effects of MPs/NPs and their potential mechanisms for reproductive toxicity, the implications of such effects on neuroactive steroids in the central nervous system are poorly investigated. In the present review we will (i) illustrate how neuroactive steroids affect brain function and (ii) review clinical and preclinical studies assessing the effects of MPs/NPs on neuroactive steroid levels, with the aim to highlight their potential implications for brain function and mental health.

Steroid hormones are synthesized from cholesterol, which translocates from the cytoplasm into the mitochondria through a process involving the Steroidogenic Acute Regulatory (StAR) protein and, in a modulatory capacity, the Translocator Protein (TSPO) 18 KDa (Porcu et al., 2016). Inside the mitochondria the enzyme CYP11A (or P450 side chain cleavage) converts cholesterol into pregnenolone, which can be further metabolized into several other steroid hormones that can be subdivided into four major classes: progestogens, estrogens, androgens, and corticosteroids (Fig. 1). Notably, the brain possesses all the enzymes necessary to locally synthesize neuroactive steroids *de novo* from cholesterol or from peripheral precursors (Stoffel-Wagner, 2003). This steroidogenic pathway is highly conserved across species, including invertebrates (Köhler et al., 2007; Lafont and Mathieu, 2007) and vertebrates (Do Rego et al., 2009; Tsutsui et al., 1999). While vertebrate steroid hormones belong to different classes (progestogens, androgens, estrogens, or glucocorticoids), invertebrate hormones are mainly ecdysteroids (especially in arthropods) involved in molting (Lafont and Mathieu, 2007). However, the presence of progesterone, estradiol, testosterone or corticosteroids, along with the enzymes necessary for their synthesis, has been documented in almost all invertebrate groups, where these steroids are involved in reproduction, development, sexual dimorphism, social behavior, and homeostasis, mostly acting through nuclear steroid receptors (Köhler et al., 2007). Likewise, within vertebrates, *de novo* steroidogenesis from cholesterol is described in fish (Pasquier et al., 2016), in the brain and peripheral sites of birds and amphibians (Do Rego et al., 2009; Tsutsui et al., 1999), as well as in mammals (Stoffel-Wagner, 2003).

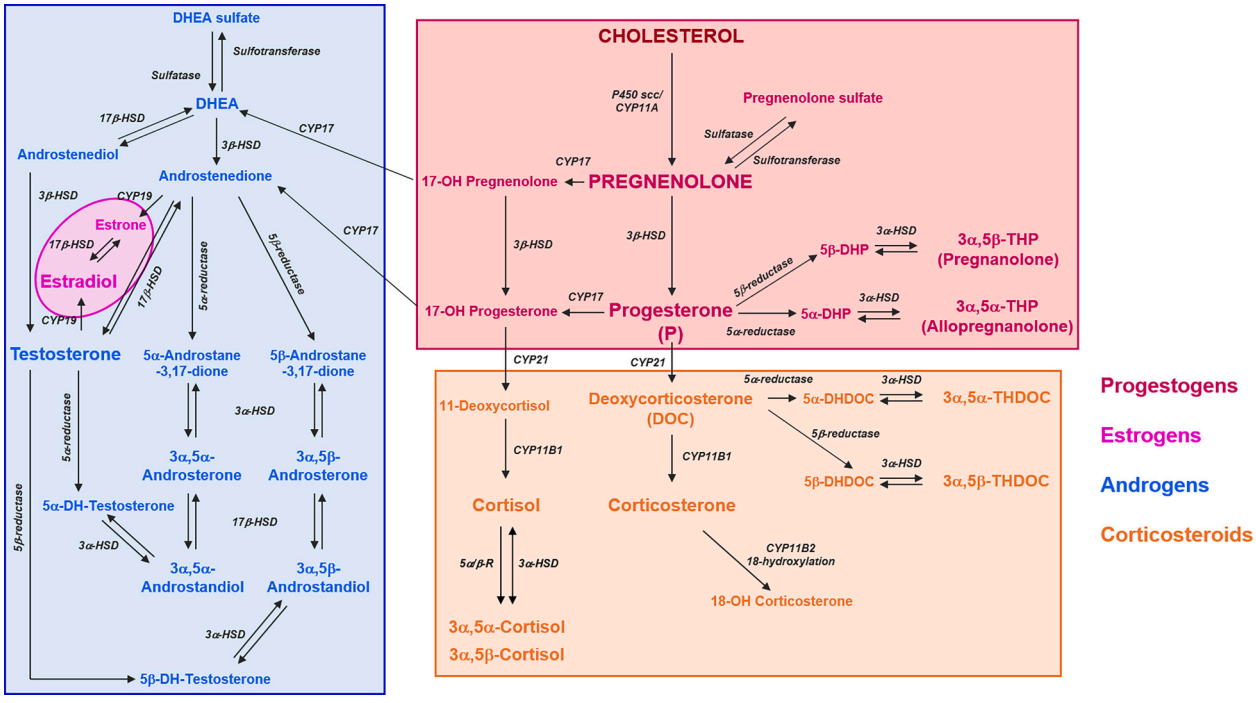

Fig. 1. Overview of the biosynthetic pathways of neuroactive steroids. Four classes can be identified: progestogens (red), estrogens (pink), androgens (blue) and corticosteroids (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.1. Progestogens

Progestogens include the steroid precursor pregnenolone, progesterone and its metabolites (3α,5α)-3-hydroxypregnan-20-one (3α,5α-tetrahydroprogesterone, or 3α,5α-THP, or allopregnanolone) and (3α,5β)-3-hydroxypregnan-20-one (3α,5β-THP or pregnanolone). Pregnenolone, the precursor for all steroids, possesses neuroactive properties on its own; specifically, it can interact with microtubule-binding proteins and with the cannabinoid receptor CB1, thus playing a role in regulating synaptic brain function, homeostasis, and behavior (Vallée et al., 2014; Vallée, 2024). Pregnenolone is converted into progesterone via a 3β-hydroxysteroid dehydrogenase (3β-HSD) enzyme (Fig. 1, red panel). Progesterone, in turn, can be converted into 5α- or 5β-dihydroprogesterone and then subsequently metabolized by 3α-HSD to form allopregnanolone or pregnanolone (Fig. 1, red panel), both of which are potent positive modulators of type A receptors for γ-aminobutyric acid ($GABA_A$ receptors) and account for most of the neuroactive effects of progesterone.

2.1.1. Allopregnanolone

The naturally occurring neuroactive steroid allopregnanolone potentiates $GABA_A$ receptors by increasing both frequency and time of channel opening (Majewska et al., 1986). $GABA_A$ receptors mediate inhibitory neurotransmission throughout the brain and are heteropentameric ion channels permeable to Cl^- ions, typically formed by two α and two β subunits coupled with one γ or δ subunit. Allopregnanolone allosterically modulates all subtypes of $GABA_A$ receptors, being more potent on the extrasynaptic $\alpha_4\beta\delta$ subtype, compared to the synaptic $\alpha_n\beta\gamma$ subtype (Carver and Reddy, 2013). In addition, it can bind to membrane progesterone receptors to activate a signaling cascade that promotes $GABA_A$ receptor phosphorylation with subsequent increased expression of extrasynaptic $\alpha_4\beta\delta$ receptors and tonic inhibition (Abramian et al., 2014). The positive allosteric modulation of $GABA_A$ receptors by allopregnanolone is thought to account for its anxiolytic, antidepressant and anticonvulsant effects (Belelli et al., 1989; Bitran et al., 1991; Khisti et al., 2000), as well as for neurogenesis in neural stem cells (Brinton, 2013).

Some of allopregnanolone's effects occur through non-GABAergic mechanisms, including: (i) neuroimmune and anti-inflammatory actions exerted via inhibition of Toll-like receptor (TLR) signaling (Balan et al., 2021); (ii) analgesic effects via inhibition of low voltage activated T-Type Ca^{2+} channels (Pathirathna et al., 2005); (iii) steroid synthesis and brain-derived neurotrophic factor expression and signaling (Serrao and Goodchild, 2022); (iv) modulation of nuclear pregnane xenobiotic receptors (Langmade et al., 2006); (v) modulation of circuit network states (Antonoudiou et al., 2022).

2.2. Estrogens and androgens

Estrogens (mainly 17β-estradiol, referred here as estradiol) and androgens (mainly testosterone and its metabolites) derive from pregnenolone metabolism into 17α-hydroxypregnenolone and then dehydroepiandrosterone (DHEA), which is further metabolized into either androstenediol or androstenedione. This latest steroid (also formed via progesterone metabolism into 17α-hydroxyprogesterone), is converted via CYP19A1 (aromatase) into estrone, which is then metabolized to estradiol by 17β-HSD; estradiol can also be synthesized by aromatization of testosterone, derived from androstenediol or androstenedione (Fig. 1, pink panel). Besides the gonads, estradiol is locally synthesized in the brain, where it rapidly alters neuronal activity and cell signaling through membrane estrogen receptors (ER) ERα and ERβ, or G protein-coupled ER, thus modulating gene expression, local protein synthesis, cytoskeletal regulation and neurogenesis (Taxier et al., 2020). As a result, estradiol modulates various brain functions, including motivated behavior and reproduction, as well as several types of learning and memory formation, consolidation and retrieval (Luine, 2014). Moreover, it affects synaptic physiology by rapidly increasing excitatory transmission as a result of an increased kinase activity, phosphorylation and surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-Methyl-D-Aspartate (NMDA) receptors, thus enhancing long-term potentiation. Finally, estradiol promotes a functional coupling of ERα and ERβ with metabotropic glutamate receptors (mGluR), which might contribute to its effects on memory consolidation, motivated behavior and sexual receptivity (reviewed in Taxier et al., 2020).

Testosterone has a weak biological activity on its own, while its metabolites are more physiologically relevant. In fact, it can be metabolized by 5α/5β-reductase into dihydrotestosterone (DHT, Fig. 1, blue panel), a more potent androgen that binds to androgen receptors (AR) with greater affinity than testosterone (Gao et al., 2005). Furthermore, DHT is a precursor for the 3α,5α/3α,5β-androstanediols that possess GABAergic properties (Katona et al., 2008), but can also bind ERs (Handa et al., 2008). Androgens act on both membrane and nuclear AR to regulate intracellular signaling and gene expression; AR are diffused throughout the brain, being particularly abundant in hippocampus and prefrontal cortex, where they are involved in synaptic plasticity, neurogenesis and spatial memory (Hamson et al., 2016; Kuwahara et al., 2021).

Both estrogens and androgens promote sexual behavior in males and females (Ågmo, 2024). Of note, in females the 3α,5α-reduced neuroactive steroids, allopregnanolone and 3α-androstanediol, also promote sexual motivation (Frye et al., 1998; Santoru et al., 2014; Sánchez Montoya et al., 2010). Moreover, estrogens and androgens influence social behavior, social interaction, social recognition, social learning, dominance status, aggression (Aspesi et al., 2025; Aspesi and Cornil, 2024). Gonadal steroids also account for sexual differentiation of the developing brain; during the perinatal period testicular secretion of testosterone in male rats promotes brain masculinization through its aromatization to estradiol, while in females the ovaries are quiescent, and lack of exposure to estradiol allows for feminization of brain development. Notably, females treated with testosterone or estradiol during this sensitive window will be sterile and sexually non-receptive and will develop masculinization of brain and behavior that persists into adulthood (McCarthy, 2008). Indeed, neonatal exposure to estradiol in female rats has enduring neuroendocrine effects in adulthood, with reduced basal levels of allopregnanolone, changes in $GABA_A$ receptor plasticity, and enhanced stress-induced allopregnanolone and extracellular dopamine content (Locci et al., 2017; Porcu et al., 2017).

2.3. Corticosteroids

Corticosteroids, mainly cortisol in humans and corticosterone in rodents, derive from progesterone, which can be converted into (i) 17-hydroxyprogesterone (via CYP17), then 11-deoxycortisol, the immediate precursor of cortisol, or (ii) it is metabolized into deoxycorticosterone (DOC), which gives rise to corticosterone via CYP11B1 (Fig. 1, orange panel). DOC can also be metabolized by 5α-reductase and 3α-HSD to give rise to (3α,5α)-3,21-dihydroxypregnan-20-one (3α,5α-THDOC, Fig. 1, orange panel) that, similarly to allopregnanolone, potentiates $GABA_A$ receptors (Majewska et al., 1986).

The main source of corticosteroids production is the adrenal gland that is part of the hypothalamic-pituitary-adrenal (HPA) axis, the main stress response system of our body that links adrenals to the brain (i.e., hypothalamus and pituitary). Acute stress leads to the release of corticotropin releasing hormone (CRH) from the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary that, in turn, stimulates adrenals to release corticosteroids. Cortisol and corticosterone can enter the brain and, by binding to glucocorticoid receptors located on the hypothalamus and pituitary, trigger a feedback mechanism to shut down HPA axis activation and restore homeostasis. Indeed, glucocorticoid receptors are widely present in limbic (hippocampus, amygdala, lateral septum) and cortical brain

regions, and all contribute to restore homeostasis following acute stress, implying that the action of corticosteroids on brain function and homeostasis is broader and goes beyond the HPA axis (Herman, 2022). Corticosteroids are indeed neuroactive steroids as they can interact with neural circuits to fine-tune brain activity. Besides the stress response, which mediates the body's reaction to physical, emotional, and metabolic stressors, corticosteroids modulate the (i) immune system, (ii) metabolism, (iii) behavior, (iv) emotional states, (v) mobilization of energy (i.e., increase in glucose availability to meet demands) and (vi) circadian rhythms (de Kloet, 2024; Herman, 2022).

Of note, in addition to corticosteroids, allopregnanolone also plays a role in negative feedback regulation of the HPA axis and contributes to restore homeostasis (Biggio et al., 2007; Pisu et al., 2022). Likewise, estradiol regulates HPA axis feedback depending on the ERs type; activation of ERα on the paraventricular nucleus of the hypothalamus inhibits glucocorticoid feedback, while ERβ activation reduces the HPA axis response to stress (Handa and Weiser, 2014).

3. Neuroactive steroids in mental disorders

Neuroactive steroids play an important role in physiological conditions related to stress/HPA homeostasis, neurodevelopment, puberty, female reproduction (i.e., the ovarian cycle, pregnancy/postpartum, menopause), and aging, and are altered in several mental diseases and brain dysfunctions.

3.1. HPA axis and stress-related neuropsychiatric diseases

Neuroactive steroids contribute to ensure appropriate physiological adaptation to external and internal stress challenges. Paradoxically, while HPA axis activation in response to acute stress is necessary to restore homeostasis and thus protect the body, its prolonged activation can lead to brain damage. A dysregulated HPA response, resulting in allostatic load, i.e. the adaptive changes in response to prolonged stress, including altered production of cortisol, catecholamines and inflammatory mediators (McEwen, 1998), is a common feature of stress-related neuropsychiatric diseases including anxiety, depression, post-traumatic stress disorder and, in females, postpartum depression, premenstrual syndrome or premenstrual dysphoric disorder (McEwen et al., 2015; Pisu et al., 2022). These diseases are also accompanied by impaired neurosteroidogenesis, with neuroactive steroid levels often correlating with severity of symptoms (Pinna and Bortolato, 2025). Altered levels of allopregnanolone and its precursors pregnenolone and progesterone were reported in several mood disorders, including anxiety/depressive disorders (Bicíková et al., 2000; Brambilla et al., 2003; Romeo et al., 1998; Schüle et al., 2014; Uzunova et al., 1998), premenstrual dysphoric disorder (Bixo et al., 2018; Girdler et al., 2001; Wang et al., 1996), postpartum depression (Deligiannidis et al., 2016; Nappi et al., 2001), posttraumatic stress disorder (Rasmusson et al., 2022; Rasmusson et al., 2006), bipolar disorder (Hardoy et al., 2006; Karademir et al., 2024), schizophrenia (Marx et al., 2006a), and eating disorder (Monteleone et al., 2001). Noteworthy, a synthetic analog of allopregnanolone, brexanolone, was the first neuroactive steroid approved in 2019 in the USA for treatment of severe postpartum depression (Meltzer-Brody et al., 2018); however, it was withdrawn from the market in 2025 in favor of zuranolone, another allopregnanolone analog that can be orally administered (Deligiannidis et al., 2023). Zuranolone is currently being evaluated in clinical trials testing its efficacy against major depression (Kato et al., 2026; Zorumski et al., 2025). Moreover, beneficial effects of pregnenolone, allopregnanolone or its synthetic analogs were reported for schizophrenia (Marx et al., 2009) and bipolar disorder (Karademir et al., 2024).

3.2. Neurodevelopment

Neurodevelopment is a highly orchestrated process during which neural cells proliferate, migrate and differentiate to give rise to the structural complexity of the brain (Bethlehem et al., 2022). By regulating neural cell proliferation and migration, as well as neurogenesis, myelination, synaptogenesis and neuroprotection, neuroactive steroids synthesized within the maternal placenta play a key role in brain development and growth (Bakalar et al., 2022; Costa, 2016; Vacher et al., 2021). It is therefore reasonable to hypothesize that early life dysregulation in their synthesis, metabolism, receptor signaling and/or downstream pathways may alter the shaping of the brain and increase the risk of developing a neurodevelopmental disorder later in life. Indeed, alterations in the levels of neuroactive steroids, particularly allopregnanolone, have been reported in children with attention deficit hyperactivity disorder (Şahin et al., 2022), as well as in young and adult males with autism spectrum disorder (Chew et al., 2021; Majewska et al., 2014). Allopregnanolone has also been involved in Tourette syndrome (Mosher et al., 2017), a neurodevelopmental disorder characterized by the presence of involuntary motor and vocal tics that typically become evident in early childhood or adolescence and can vary in type and severity, often worsening with stress or excitement (Leckman et al., 2010). While no study has investigated so far a potential association between allopregnanolone levels and Fragile X syndrome (another neurodevelopmental disorder), one study reported its ability to improve plasma metabolomic profile associated with GABA metabolism in Fragile X-associated tremor/ataxia syndrome, a late-onset neurodegenerative disorder (Napoli et al., 2019).

Importantly, besides allopregnanolone, other neuroactive steroids, including cortisol, androsterone, pregnenolone, DHEA and their sulfate conjugates were found to be altered in male children with autism spectrum disorder (Gao et al., 2022; Majewska et al., 2014). Consistently, gain-of-function and missense variants in the pregnenolone sulfate-sensitive plasma membrane cation channel TRPM3 (Transient Receptor Potential Melastatin 3) has been reported to underlie a spectrum of neurodevelopmental disorders (Burglen et al., 2023), including intellectual disability and epilepsy (Van Hoeymissen et al., 2020; Zhao and Rohacs, 2021), developmental and epileptic encephalopathies (Kang et al., 2021), global developmental delay and hypotonia (Lines et al., 2022), cerebellar atrophy (Dyment et al., 2023), neurodevelopmental delay and cerebral palsy (Sundaramurthi et al., 2023), behavioral abnormalities and cognitive impairment (Pawelak et al., 2024).

Finally, the synthetic neuroactive steroid ganaxolone has been approved in the USA to treat seizures in patients with cyclin-dependent kinase-like 5 deficiency disorder, a rare, X-linked developmental and epileptic encephalopathy characterized by early-onset epilepsy (refractory seizures), developmental delays (motor, cognitive, speech), visual impairment and hypotonia (Downs et al., 2024; Knight et al., 2022). Indeed, ganaxolone has been proposed as a safe innovative neonatal therapy for seizure control and neuroprotection when administered early following birth-related hypoxia, being able to prevent or reduce the incidence of the enduring disabilities associated with preterm birth, cerebral palsy, and epilepsy (Yawno et al., 2017). It has also shown therapeutic potential in a mouse model of Angelman syndrome, a rare neurogenetic disorder characterized by severe intellectual disability, developmental delays, jerking movements (ataxia), sleep problems and epilepsy (Ciarlone et al., 2017).

3.3. Neurodegenerative diseases

Neuroactive steroid levels are altered in several neurodegenerative diseases, both in experimental models and in patients. For instance, dysregulated neurosteroidogenesis has been reported in Parkinson's disease rodent models of nigrostriatal dopaminergic neurons degeneration (Bourque et al., 2016; Melcangi et al., 2012), with estrogens, progesterone and inhibitors of 5α-reductase showing neuroprotective actions on the nigrostriatal dopaminergic system in preclinical and clinical studies (Bourque et al., 2016; Bourque et al., 2024; Dluzen and

Horstink, 2003; Sheibani et al., 2022), likely through both genomic and non-genomic mechanisms (Bourque et al., 2009). In humans, levels of allopregnanolone and its precursor 5α-dihydroprogesterone are decreased in plasma and cerebrospinal fluid of Parkinson's disease patients (di Michele et al., 2003), and changes in neurosteroidogenic enzymes were observed in the substantia nigra and caudate nucleus of parkinsonian patients (Luchetti et al., 2010). Interestingly, allopregnanolone and 5α-dihydroprogesterone showed neuroprotective effects in slice cultures from Parkinson's disease patients (Luchetti et al., 2023), suggesting that restoration of neuroactive steroid imbalance might represent a useful therapeutic approach.

Age-related changes in neuroactive steroid levels were also reported in animal models of Alzheimer's disease (Caruso et al., 2013). Likewise, when comparing Alzheimer's patients with aged nondemented controls, compelling evidence pointed to altered neurosteroidogenesis in Alzheimer's patients, with a significant increase in pregnenolone and DHEA levels in the cerebrospinal fluid as well as in hypothalamus, hippocampus, frontal and temporal cortex, and a significant reduction of (i) pregnenolone sulfate and DHEA sulfate in the striatum and cerebellum, (ii) DHEA sulfate in the hypothalamus, and (iii) allopregnanolone in the temporal cortex (Kim et al., 2003; Luchetti et al., 2011; Marx et al., 2006c; Naylor et al., 2010; Weill-Engerer et al., 2002). The majority of preclinical studies showed some promise for potential benefits of progesterone, allopregnanolone, estrogens and, to a certain degree, androgens (either directly or through the aromatization into estrogens) as neuroprotective agents in Alzheimer's disease (Białek et al., 2004; Correia et al., 2010; Divya et al., 2025; Som et al., 2022; Vuic et al., 2025; Wang et al., 2007). However, chronic allopregnanolone treatment was also reported to accelerate disease pathogenesis in three different mouse models (Bengtsson et al., 2013; Bengtsson et al., 2012), suggesting that its effects might be influenced by strain or genetic background.

Finally, alterations in neurosteroidogenesis have also been reported in other neurological diseases, including multiple sclerosis (Nesbitt et al., 2025; Noorbakhsh et al., 2014), neuropathic pain (Meyer et al., 2019), cerebral ischemia (Vahidinia et al., 2020), traumatic brain injury (Verdoorn et al., 2023), and spinal cord injury (Guennoun et al., 2015). Given that neuroactive steroids exert neuroimmune and anti-inflammatory effects (Balan et al., 2019) and promote neural stem cell and oligodendrocyte proliferation (Brinton, 2013), they might be a novel and valuable therapeutic intervention for those neurological diseases associated to increased neuroinflammation and altered endogenous neuroactive steroid levels.

3.4. Substance use disorders

Acute administration of several drugs of abuse, including alcohol (Romeo et al., 1996; VanDoren et al., 2000), nicotine (Concas et al., 2006; Marx et al., 2006b; Porcu et al., 2003), cannabis (Grobin et al., 2005; Vallée et al., 2014), cocaine (Grobin et al., 2005; Milivojevic et al., 2019) and morphine (Concas et al., 2006), alters brain and plasma levels of allopregnanolone and its precursors in both rodents and humans. In turn, allopregnanolone is able to exert rewarding effects (Finn et al., 1997) and to influence the rewarding properties of drugs (Ford et al., 2007; Morrow et al., 2006; Sinnott et al., 2002). Indeed, this neuroactive steroid modulates alcohol or cocaine intake, and reduces reinstatement and withdrawal severity (Finn et al., 2010; Ford et al., 2007; Milivojevic et al., 2019; Morrow et al., 2020; Morrow et al., 2006; Sinnott et al., 2002). By contrast, under chronic exposure, the allopregnanolone response is blunted for alcohol (Morrow et al., 2020), nicotine or morphine (Concas et al., 2006). It has been hypothesized that alcohol-induced elevations of neuroactive steroids in brain after acute exposure may affect ethanol sensitivity, thus preventing excessive alcohol consumption. Under chronic exposure, both the neuroactive steroid response and sensitivity to ethanol are lost, leading to an increased risk of excessive drinking. Thus, administration of neuroactive steroids or other therapies able to promote neurosteroidogenesis may restore ethanol sensitivity in alcohol-dependent patients (Morrow et al., 2020). The neuroactive steroid precursor pregnenolone has also been proposed as a valuable therapeutic approach for substance use disorder as it improves craving, anxiety and autonomic responses to stress in humans with alcohol (Milivojevic et al., 2023) and cocaine (Milivojevic et al., 2022) use disorders. Moreover, pregnenolone rescues tetrahydrocannabinol-induced deficits in an animal model of prenatal cannabis exposure (Serra et al., 2024). Indeed, for its ability to allosterically modulate cannabinoid CB1 receptors, pregnenolone has also been proposed as a therapeutic option for cannabis intoxication. Preclinical studies in mice have shown that pregnenolone decreased self-administration of the CB1 receptor agonist WIN 55,212–2 (Vallée et al., 2014) and prevented psychotic-like effects of tetrahydrocannabinol (Busquets-Garcia et al., 2017). Due to its short half-life, low oral bioavailability and metabolism into downstream steroids, novel synthetic analogs have been developed, with the AEF0117 compound appearing the most promising in reducing cannabis intake and its associated behavioral impairments in animals and humans (Haney et al., 2023).

Chronic exposure to drugs of abuse also targets cortisol/corticosterone and the HPA axis that is initially activated, thus leading to increased CRH signaling in the hypothalamus and in extra-hypothalamic regions, which might contribute to *hyperkatifeia*, the condition of increased negative affect and motivation during withdrawal and escalation of intake (Koob, 2021). In agreement, preclinical studies suggested that blocking CRH signaling might ameliorate withdrawal symptoms and prevent relapses, thus representing a useful therapeutic approach for alcohol use disorders (Zorrilla et al., 2014). Noteworthy, in addition to CRH antagonists, allopregnanolone also exerts an inhibitory action on CRH signaling, which might represent another mechanism through which this neuroactive steroid might exert its therapeutic potential for alcohol use disorder (Morrow et al., 2020).

Estradiol is well known to influence perception of rewarding stimuli, either natural, such as food (Richard et al., 2017), or drugs of abuse, including nicotine (Franklin et al., 2022), alcohol (Hilderbrand and Lasek, 2018), cocaine (Segarra et al., 2010), amphetamine (Justice and de Wit, 2000) and opioids (Ethridge and Smith, 2023). The notion that sex hormones are crucial regulators of reward and motivation is further supported by the finding that the menstrual cycle modulates reward sensitivity and reinforcement learning in young women (Diekhof and Ratnayake, 2016), regulates the ability to wait for the optimal response time to maximize reward (Reimers et al., 2014), influences operant performance and sexual activity (Bonsall et al., 1978) and affects consumption of drugs (Joyce et al., 2021).

4. Do MP/NPs affect neuroactive steroids levels?

Exposure to MPs/NPs alters steroidogenesis as a result of different mechanisms involving a direct action on gene expression of steroidogenic enzymes and effects on the HPA and hypothalamic-pituitary-gonadal (HPG) axes, with subsequent alterations in cortisol/corticosterone levels and sex steroids, respectively (Ullah et al., 2023). Here we summarize the effects of MPs/NPs on neuroactive steroid levels across different species. We focus on exposure to selected types of MPs and NPs that can be easily monitored under laboratory conditions, not on the endocrine disrupting effects of MPs/NPs additives, whose effects are comprehensively reviewed elsewhere (Li et al., 2024a). Search keywords included “steroid name” and MP or NP, or the specific plastic type, i.e. polyamide (PA), polyethylene (PE), polyester (PES), polystyrene (PS), polypropylene (PP), or polyvinyl chloride (PVC). Results are summarized in Table 1.

In general, effects of MPs/NPs on steroid levels vary across species, sex, age, type of MPs/NPs, particle size, length of exposure and doses tested. Almost all the studies conducted so far have focused on peripheral levels of steroids, while brain levels have been almost ignored.

Table 1
Effects of MPs and NPs on steroid levels across different species.

MP/NP Type	MP/NP Size	Dose and duration of exposure	Animal model	Effects on steroid levels or steroidogenic enzymes	References
PA, PE, PP, PS, EPS, PTFE	Unspecified size	50.56 particles/individual, EPS-contaminated gravel shore	Wharf roach (*Ligia exotica*)	• Brain (whole head): decreased progesterone and increased cortisol	Choi et al., 2023
PA, PMMA	5 μm Ø fluorescent particles	0.1 and 0.5 mg/day, oral gavage, 28 days	Male ICR mice, 4 weeks old	• Serum and testis: decreased testosterone with 0.5 mg/d PA; no effect of the other treatments	Zhang et al., 2024b
PA	5 μm Ø powder	Inhalation of 9.53 mg/m^3 over 4.35 h	Female Sprague-Dawley rats, 8–10 weeks old	• Plasma: decreased estradiol and no change in progesterone, 24 h after inhalation	Cary et al., 2023
PE	0.2–1 mm Ø particles	0.1, 1 and 10 mg/L, 15 and 30 days	Freshwater fish (*Tor putitora*), unspecified sex and age	• Serum: increased cortisol	Ullah et al., 2026
PE	22–71 μm Ø particles	4, 8, 16, 32 and 64 mg/L, 7 or 14 days	Crucian carp (*Carassius carassius*), unspecified sex and age	• Gill, intestine and liver: increased cortisol at ≥32 mg/L	Yu et al., 2026
PE	25 μm Ø	100 μg/L, 35 days	Male and female AB strain zebrafish (*Danio rerio*), adult exposure followed by mating; outcomes evaluated in F1 offspring embryo	• Serum: increased estradiol in males and no change in females; decreased testosterone and 11-ketotestosterone in females and no change in males	Xue et al., 2024a
PE	0.3–0.6 mm Ø LDPE powder	1% in the diet	Male and female Atlantic cod (*Gadus morhua*), 4 years old	• Plasma: no change in estradiol, testosterone and 11-ketotestosterone	Fernández-Míguez et al., 2023
PE	34–50 μm Ø particles	60 mg/L (density 1.036–1.067 × 10^7 particles/L) in the water tank, 10 days	Frog (*Xenopus laevis*) larvae, developmental stage NF 45 to NF57	• Tail: increased corticosterone	Ruthsatz et al., 2023
PE	34–50 μm Ø particles	60 mg/L (density 1.036–1.067 × 10^7 particles/L) in the water tank, 10 days	Frog (*Xenopus laevis*) larvae, developmental stage NF46 to NF57	• Tail: no change in corticosterone	Martin et al., 2025
PE	10–90 μm Ø particles	20 mg/kg, oral gavage, 28 days	Female C57BL/6 J mice, 6 weeks old	• Serum: decreased testosterone	Wang et al., 2026
PE	Unspecified size	1.5 mg/kg, oral gavage, 56 days	Male Albino rats, unspecified age	• Serum: decreased testosterone • Testis: decreased StAR, 3β-HSD and 17β-HSD expression	Ijaz et al., 2024; Ijaz et al., 2023b
PE	4–6 μm Ø average	3.75, 15, and 60 mg/kg/day, oral gavage, 35 days	Male Sprague-Dawley rats, 10 weeks old	• Serum: decreased cortisol and increased adrenocorticotropic hormone	Farag et al., 2024
PE	34–50 μm Ø particles	1.5 mg/kg, oral gavage, 28 days	Male Wistar rats, 8–12 weeks old	• Serum: decreased testosterone	Kehinde et al., 2024
PE	42 μm Ø particles	15 and 60 mg/kg, oral gavage, 28 days	Male Wistar rats, 8 weeks old	• Serum: decreased testosterone	Kehinde et al., 2026
PEG	Unspecified size; PEG-b-PLA	20 and 40 mg/kg, (2 mg/ml ultrapurified water), intraperitoneal	Female Wistar rats, treated at PND 4–7, tested at PND 176 *(~25 weeks old)*	• Serum: increased progesterone at the 20 mg/kg dose	Rollerova et al., 2015
PET	100 μm Ø microfibers	0.0005, 0.1, 1, 10, and 100 mg/L, 32 days	Wild Mediterranean mussels (*Mytilus galloprovincialis*), transferred to the lab, 14 days acclimation	• Hemolymph: decreased estradiol and testosterone in all groups	Choi et al., 2022
PET	50–100 μm Ø, mechanical grinding of water bottles	5 mg/week in food, 29 weeks from 5 to 34 weeks of age	Male C57BL/6 N mice, 4 weeks old (up to 34 weeks old)	• Serum: decreased testosterone	Jeong et al., 2025
PET, PS	PET 240 nm Ø, PS 220 nm Ø	PET 0.1, 1 and 10 μg/ml; PS 1, 10 and 100 μg/ml	Ovarian follicle cell cultures (96 h) from female CD-1 mice, PND 30–38 *(~4–5 weeks old)*	• Cell medium: increased pregnenolone; no change in progesterone, estradiol, testosterone and androstenedione. Decreased StAR and Cyp17a1, increased Cyp19a1 mRNA expression	Alahmadi et al., 2025
PE, PET, PS	~ 3000 μm Ø; PE 0.961 g/mL, PS 1.04 g/mL, PET 1.370 g/mL	2.8 mg/L; 700 mg of each type/tank (22 PET, 25 PS and 28 PE pellets/tank), 113 days (from fertilized egg to mobile yolk-sack larvae)	Sea trout (*Salmo trutta*) embryo	• Whole body: no change in corticosterone, dehydrocorticosterone and cortisone	Jakubowska et al., 2020
PE, PP	10–98 μm Ø	60 mg/L, 6 weeks	Wrinkled frogs (*Glandirana rugosa*), juvenile, unspecified sex	• Saliva: increased corticosterone in both PP and PE groups	Park and Do, 2025
PE, PP	3 mm, <125 μm, and 3 mm-125 μm Ø, mixtures from plastic items collected in the coast	Feeding every 3rd day, starting with 4 days at 25 mg, 4 days at 50 mg and 4 days at 75 mg up to 5 weeks of treatment for a total amount of 600 mg. Dose of PE-PP/g body mass reached 2.7 at the end of the experiment	Male and female Japanese quail (*Coturnix japonica*), 1 week old, at the beginning (sexual maturity at week 5 of life, i.e. week 4 of treatment)	• Plasma: decreased estradiol in females with the 3 mm and the 3 mm-125 μm size; no change in testosterone in males in any condition	Monclús et al., 2022
PE, PVC	PE 200 nm Ø, PVC 5000 nm Ø particles dissolved in 0.1 M PBS	PE 0.03, 0.3 and 3 mg/day, PVC 0.06, 0.6 and 6 mg/day, oral gavage (100 μl/mouse), 2 weeks	Female C57BL/6 J mice, PND 21 *(3 weeks old)*	• Serum: no change in estradiol	Zang et al., 2025

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Table 1 (*continued*)

MP/NP Type	MP/NP Size	Dose and duration of exposure	Animal model	Effects on steroid levels or steroidogenic enzymes	References
PES	average Ø of microfibers 157.68 μm (17.66–476.72 μm)	500, and 1000 fibers/L, 21 days	Male medaka (*Oryzias latipes*), adult	• Plasma: increased estradiol with a peak occurring at day 3 of exposure	Kim et al., 2023b
PS	75 nm Ø, concentration 2.5% (*w/v*) 1.06 × 1013 particles/mL	5, 10, 20, and 40 mg/L, 28 days	Shrimp (*Macrobrachium nipponense*), juvenile	• Serum: increased progesterone, estradiol and testosterone at 5 mg/L; decreased at 20 and 40 mg/L	Li et al., 2023
PS	500 nm and 30 μm Ø	0.29 mg/L, 14 days	Clams (*Telligarca granosa*), adult	• Plasma: no change in cortisol	Shi et al., 2020
PS	100 nm Ø, 2.5% aqueous suspension, 1.05 g/cm^3 density	0.2, 2 and 4 mg/L, 14 days	Pearl spot (*Etroplus suratensis*), juvenile, unspecified sex	• Plasma: dose-dependent increased cortisol	Das et al., 2025
PS	1 μm Ø, aqueous suspension with 1.05 g/cm^3 density	0.01, 0.1 and 1 mg/L, 14 days	Nile tilapia (*Oreochromis niloticus*), unspecified age and sex	• Plasma: increased cortisol	Das et al., 2023
PS	Unspecified size, density of 1.50 g/cm^3	0.5 mg/L, 1 mg/L and 2 mg/L, 15 days	Silver carp (*Hypophthalmichthys molitrix*), juvenile, unspecified sex	• Plasma: dose-dependent increased cortisol	Zaman et al., 2024
PS	44 nm Ø	100 μg/L, 30 days	Goldfish (*Carassius auratus*), adult, unspecified sex	• Plasma, no change in cortisol	Brandts et al., 2022
PS	1 μm Ø	10 and 100 beads/L, 6, 12, 24, 72 and 120 h exposure	Goldfish (*Carassius auratus*), unspecified age and sex	• Plasma: increased cortisol at both doses, with a peak at 72 h exposure	Kim et al., 2023a
PS	25 nm Ø, 1.05 g/cm^3	0.2, 2, and 20 mg/L, 2 days	AB/TL strain zebrafish larvae	• Whole body: increased cortisol at 2 and 20 mg/L doses	Brun et al., 2019
PS	Unspecified size; lab synthesized PS	100, 500, and 1000 mg/L in food pellets, 30 days	Zebrafish, unspecified strain, age and sex	• Whole body: dose-dependent increase in cortisol	Ahmadifar et al., 2024
PS	Unspecified size; lab synthesized PS	0.1, 1, and 10 mg/L, 28 days	Female Tuebingen strain zebrafish, adult	• Whole body: increased cortisol, and decreased estradiol and testosterone at all doses tested	Mohammadzadeh et al., 2024
PS	100 nm Ø, 100 mg/ml in sterile deionized water	50 and 100 μg/L, 15 days	Female AB-strain zebrafish, adult	• Blood: decreased estradiol and testosterone	Adhikari et al., 2025
PS	100 nm Ø, 100 mg/ml in deionized water	40.1 μg/L/day, 21 days and 3 months	Female AB strain zebrafish, 3 months old	• Serum: decreased estradiol • Brain and ovary: increased testosterone at 21 days • Ovary: downregulated CYP19A1A, 17β-HSD, 20β-HSD and upregulated 3β-HSD gene expression at 3 months	Adhikari et al., 2024
PS	1 μm Ø, 2.5% w/v in ultrapure water	100 μg/L (5.32 × 10^{14} particles/L), 60 days	Male and female AB strain zebrafish, 3 months old	• Plasma: no change in estradiol and testosterone in both sexes	Lin et al., 2023
PS	50 nm Ø particles, 10% suspension in deionized water	1 mg/L, 21 days	Male and female AB-strain zebrafish, 4 months old	• Plasma: no change in estradiol • Ovary: no change in estradiol and testosterone	Ye et al., 2024
PS	80 nm Ø particles, 1% suspension	0.1 and 1 mg/L, 14 days	Male and female AB-strain zebrafish, 4 months old	• Plasma: decreased estradiol in females and no change in males; decreased testosterone in females and males • Testis: decreased 17β-HSD, CYP11a, CYP19a	Chen et al., 2025
PS	~ 53 μm Ø, lab synthesized	0.02 and 20 mg/L, 96 h	Seabass (*Dicentrarchus labrax*), juvenile, unspecified sex	• Plasma and mucus: no change in cortisol	Brandts et al., 2021
PS	10 μm Ø, 2.5% w/v, as dispersion	2, 20 and 200 μg/L, 60 days	Male and female marine medaka (*Oryzias melastigma*), 3 months old	• Plasma: estradiol and testosterone decreased in females and increased in males at 200 μg/L	Wang et al., 2019
PS	10 μm Ø, 3.06 × 10^6 beads/ml	18, 180 and 1800 MP/ml, in the aquatic portion of the cage, 6 weeks	Male and female pond frogs (*Pelophylax nigromaculatus*), juvenile	• Saliva: trend for increased corticosterone	Park et al., 2024
PS	100 nm Ø, 25 mg/ml, suspension in double-distilled water	10 mg/ml/day, intragastrically, 28 days	Male BALB/c mice, 3 weeks old	• Serum: decreased testosterone • Leydig cells: decreased StAR, CYP11A1 and 3β-HSD protein	Cai et al., 2023
PS	60 nm Ø, in purified water	1 and 100 mg/kg/day, oral gavage, 14 days	Male BALB/c mice, 4 weeks old	• Serum, testis and TM3 Leydig cell lines: decreased testosterone at the higher dose	Liu et al., 2026
PS	50 nm, 5 μm and 50 μm Ø, 2.5% w/v in deionized water	5 mg/kg of each size, oral gavage, 8 weeks	Male BALB/c mice, 5 weeks old	• Serum: decreased testosterone at the 50 μm size	Qu et al., 2024
PS	4 μm Ø, 10 mg/mL density	45 mg/kg/day, oral gavage, 28 days	Male BALB/c mice, 6 weeks old	• Plasma: trend for decreased testosterone • Testis: trend for decreased StAR, CYP11A1, CYP17A1, 3β-HSD and 17β-HSD mRNA expression	Liu et al., 2023
PS	0.5, 4, 10 μm Ø, 1% w/v solution in 10 ml	1000 μg/L, in drinking water, 180 days	Male BALB/c mice, 6 weeks old	• Serum: decreased testosterone	Jin et al., 2024

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Table 1 (*continued*)

MP/NP Type	MP/NP Size	Dose and duration of exposure	Animal model	Effects on steroid levels or steroidogenic enzymes	References
PS	20 nm Ø, in distilled water	50 mg/kg/day, oral gavage, 28 days	Male BALB/c mice, 6 weeks old	• Serum and TM3 Leydig cell lines: no change in testosterone	Wu et al., 2026
PS	5 μm Ø, in deionized water	11, 22, and 44 mg/kg/day, oral gavage, 28 days	Male BALB/c mice, 7–8 weeks old	• Serum: increased estradiol at the higher dose; decreased testosterone at 22 and 44 mg/kg	Zhao et al., 2025b
PS	60 nm Ø, 1% (w/v) in deionized water	10, 50 and 100 mg/kg/day, oral gavage, 14 days	Male C57BL/6 J mice, PND 21 *(3 weeks old)*	• Serum: decreased testosterone • Testis: decreases StAR and CYP11A1 expression	Zhao et al., 2025a
PS	5 μm Ø, 1% w/v in 10 ml deionized water	0.25, 0.5, 1 mg/day, oral gavage, 4 weeks	Male C57BL/6 mice, 6 weeks old	• Serum: decreased testosterone • Testis: dose-dependent decrease in StAR, CYP11A1, and 3β-HSD mRNA expression	Liu et al., 2024
PS	5 μm Ø, 1% w/v in 10 ml saline	0.25, 0.5, and 1 mg/d, oral gavage, 4 weeks	Male C57BL/6 mice, 6 weeks old (*as in* Liu et al., 2024)	• Serum: decreased corticosterone at 0.5 and 1 mg/d doses • Adrenals: decreased StAR, CYP11A1 and 3β-HSD expression	Xiong et al., 2025
PS	100 and 500 nm Ø	0.1 g/kg in chow diet; 500 nm equals to 14.4 mg/kg/day; 180 day exposure, followed by 50-day recovery	Male C57BL/6 mice, 6–8 weeks old	• Serum: increased testosterone after treatment • Testis: increased CYP11A1, CYP17A1, and 17β-HSD protein; decreased StAR and 3β-HSD protein • All effects normalized following 50-day recovery	Lu et al., 2025
PS	40 and 200 nm Ø fluorospheres	0.1 mg/day (4.42×10^{10} 40 nm + 2.16×10^{8} 200 nm), oral administration, 5 weeks	Male C57BL/6 mice, 8–10 weeks old	• Serum: decreased testosterone	Nikolic et al., 2022
PS	~50.7 nm Ø, 1.05 g/ml, suspended in double-distilled water 10 ml/kg	2.5 mg/kg/day, oral gavage, 90 days	Male C57BL/6 J mice, 3 and 17 months old *(~13 and 73 weeks old)*	• Serum and primary Leydig cell cultures: decreased testosterone in young mice	Feng et al., 2025
PS	<50 μm Ø, grinded aged particles	2 mg/kg/day, 28 days	Male and female C57BL/6 mice, unspecified age	• Serum: increased estradiol in females and no change in males • Ovary: increased StAR, 3β-HSD and 17β-HSD mRNA expression • Testis: no change in 3β-HSD and 17β-HSD mRNA expression	Yang et al., 2022
PS	5 μm Ø, 1.46×10^{6} particles suspended in ultrapure water	0.1 mg/day in 0.2 ml, oral gavage, 30 or 44 days	Male and female C57BL/6 mice, 5 weeks old, tested after mating (30 days exposure) or later (44 days exposure)	• Serum: estradiol decreased in females and increased in males; testosterone increased in females and decreased in males	Wei et al., 2022
PS	500 nm Ø particles	100 and 1000 μg/L in tap water, 29 days	Female C57BL/6 J mice, PND 40–60 *(~5–8 weeks old)*	• Serum: decreased progesterone at 1000 μg/L; no change in estradiol	Gholiof et al., 2025
PS	50 nm Ø particles in deionized water (10% suspension)	2.5 mg/kg in 5% DMSO, 28 days	Ovariectomized female C57BL/6 J mice, 8 weeks old	• Serum and mammary gland: no change in estradiol	Li et al., 2026
PS	50 and 90 nm Ø, dispersed in deionized water, 50 mg/mL	3 and 15 mg/kg/day of each size, oral gavage, 30 days	Male ICR mice, 4 weeks old	• Serum: decreased testosterone (except for the 3 mg/kg-90 nm group)	Fu et al., 2023
PS	20 nm Ø	50 μg/kg/day via tail vein, 2 days	Male ICR mice, 6 weeks old	• Serum: decreased testosterone • Testis: decreased testosterone and StAR protein	Sui et al., 2023
PS	0.1 μm Ø, 2.5% w/v	30 mg/kg/day, 4 days	Male ICR mice, 6–8 weeks old	• Plasma: decreased testosterone • Testis: decreased testosterone and StAR and CYP11A1 mRNA expression	Li et al., 2024b
PS	100 nm Ø, in saline	15, 30 and 60 mg/kg/day, oral gavage, 6 weeks	Female ICR mice, 6 weeks old	• Serum: decreased estradiol	Hu et al., 2026
PS	0.5 μm Ø	0.5 mg/L (~ 7.18×10^{9} particles/L), 5 mg/L (~7.18×10^{10} particles/L), and 50 mg/L (~7.18×10^{11} particles/L), in drinking water from day 1 of pregnancy	F0 female ICR mice exposed during pregnancy; test on their male offspring at PND 35 and PND 70 *(5 and 10 weeks old)*	• Serum: decreased testosterone at the higher dose in PND 35 mice, and at all doses in PND 70 mice	Zhao et al., 2023
PS	1 μm Ø	1.357 μg/g/day and 1.357 ng/g/day, oral gavage, from birth to weaning	F0 female ICR mice exposed during lactation, and non-exposed F1 and F2 generations; samples collected in 4 months old mice *(~17 weeks old)*	• Serum: increased testosterone and no change in progesterone and estradiol in F0 females • Ovary: upregulation of CYP17A1 expression in F0 females • Serum: decreased testosterone in F1 (but not F2) males	Dou et al., 2024

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Table 1 (*continued*)

MP/NP Type	MP/NP Size	Dose and duration of exposure	Animal model	Effects on steroid levels or steroidogenic enzymes	References
PS	0.1 and 1 μm Ø	0.1, 1 and 0.1 + 1 μm (100 mg/kg/day) in 10 ml/kg deionized water, oral gavage, 5 days/week to mimic subchronic exposure, 5 weeks	Male Kunming mice, 5 weeks old	• Serum: decreased testosterone	Zhang et al., 2023
PS	Unspecified size	1 mg/day, oral gavage, 42 days	Female Kunming mice, 4 weeks old	• Serum: decreased estradiol • Ovary: decreased CYP11A, CYP19A, StAR, Stard5, Ldlr, Lhcgr, and Scarb1 gene expression	Xue et al., 2024b
PS	50–90 nm Ø	0.5 and 1 mg/kg/day, oral gavage, 90 days after which mating occurred	Female Kunming mice, ~8 weeks old, early pregnant	• Serum: increased progesterone in the 1 mg/kg group; increased estradiol in both 0.5 and 1 mg/kg groups	Qiao et al., 2025
PS	2 μm Ø in deionized water	0.01, 0.1, and 1 mg/kg/day, oral gavage, 42 days	Male NMRI mice, 6 weeks old	• Serum: decreased testosterone	Zangene et al., 2024
PS	2–135 μm Ø, naturally-aged particles in 10% ethanol/ ultrapure water	10 mg/kg/day, oral gavage, 21 days	Female Swiss mice, 8–10 weeks old	• Serum: no change in corticosterone	Barichello et al., 2025
PS	Unspecified size	0.01 mg/kg in 0.01% DMSO, oral gavage, 56 days	Male Albino rats, 6–8 weeks old	• Plasma: decreased testosterone • Testis: decreased StAR, 3β-HSD and 17β-HSD mRNA expression	Hamza et al., 2023
PS	100 nm Ø, density 1.284 g/ cm^3	0.01 mg/kg, oral gavage, 56 days	Male Albino rats, 250 g *(~6–8 weeks old)*	• Plasma: decreased testosterone • Testis: decreased StAR, 3β-HSD and 17β-HSD mRNA expression	Ijaz et al., 2023a
PS	Unspecified size	0.01 mg/kg, oral gavage, 56 days	Male Albino rats, 8–12 weeks old	• Plasma: decreased testosterone • Testis: decreased StAR, 3β-HSD and 17β-HSD expression	Akbar and Ijaz, 2024
PS	100 nm Ø	0.01 mg/kg, orally, 8 weeks (56 days)	Male Sprague-Dawley rats, 200 g *(~6–8 weeks old)*	• Plasma: decreased testosterone • Testis: decreased StAR, 3β-HSD and 17β-HSD mRNA expression	Rizwan et al., 2023
PS	0.4–0.6 μm Ø	5 mg/kg, oral gavage, 8 weeks	Male Sprague-Dawley rats, 7 weeks old	• Plasma: decreased testosterone	Hwang et al., 2024
PS	1 μm Ø	0.5 and 2 mg/kg/day, oral gavage, 28 days	Female Sprague-Dawley rats, 3 weeks old	• Serum: decreased progesterone and estradiol • Ovary: decreased CYP19A1 and StAR mRNA expression	Wang et al., 2023
PS	Unspecified size	2.5 mg/kg/day, oral gavage, 6 weeks	Female Sprague-Dawley rats in the diestrus phase, PND 28 *(4 weeks old)*	• Serum: decreased progesterone and estradiol	Amran et al., 2023
PS	3–5 μm Ø	3 and 30 mg/kg, in the diet, exposure during pregnancy and lactation	Female Sprague-Dawley rats, 9 weeks old, exposed during pregnancy and lactation; test on F1 and F2 male offspring, 17 weeks old	• Serum: decreased testosterone in F1 at both doses and in F2 at the higher dose • Testis: decreased StAR, 3β-HSD, 17β-HSD and Cyp11a1 in F1; increased StAR in F2	Jiang et al., 2026
PS	100 nm Ø, in deionized water	1.5, and 75 mg/kg/day, oral gavage, 28 days	Male Wistar rats, 5 weeks old	• Serum: decreased testosterone at 75 mg/kg	Wang et al., 2024
PS	500 nm Ø, in distilled water	0.15 and 1.5 mg/day, oral gavage, 60 days	Male Wistar rats, PND 45 *(~6 weeks old)*	• Serum: no change in testosterone	Valencise et al., 2025b
PS	25 and 50 μm Ø	1, 3, 6, and 10 mg/kg/day in distilled water, oral gavage, 35 days	Male Wistar rats, 190 g *(~6–7 weeks old)*	• Serum: increased cortisol	Babaei et al., 2022
PS	25 nm Ø, dissolved in distilled water	3, and 10 mg/kg/day, oral gavage (in 5 ml), 60 days	Male Wistar rats, 150–180 g *(~6–7 weeks old)*	• Plasma: decreased testosterone at both doses	Ebrahim et al., 2024
PS	5 μm Ø, 1 mg/5 ml distilled water	0.1 mg/g/day, oral gavage, 30 days	Male Wistar rats, ~8 weeks old	• Testis: decreased testosterone; decreased StAR, 3β-HSD and 17β-HSD expression	Falvo et al., 2025
PS	<100 nm Ø, in distilled water 133.3 μg/ml	200 μg/kg/day, oral gavage, 55 days	Male Wistar rats, 8–10 weeks old	• Serum: decreased testosterone • Testis: decreased 3β-HSD and 17β-HSD expression	Setiyowati et al., 2026
PS	5 μm Ø, in distilled water	0.1, 1, 10, 20 and 40 μg/kg/day, oral gavage, 45 days	Male Wistar rats, 9–12 weeks old	• Plasma: decreased testosterone	Alsenousy et al., 2026
PS	500 nm Ø	0.015 mg/day in 0.3 ml distilled water, oral gavage, 25 days	Female Wistar rats, PND 45–60 *(~6–8 weeks old)*	• Serum: decreased progesterone; no change in estradiol • Ovary: decreased StAR expression	Valencise et al., 2025a
PS	Unspecified size; dispersion in ultrapure water, 1.5×10^6 particles/day	0.1 mg/day, oral gavage for 4 estrus cycles (24–26 days)	Female Wistar rats, adult ~196 g *(~9 weeks old)*	• Serum: decreased estradiol during the estrus phase	Haddadi et al., 2022
PS	2–5 mm Ø pellets cryofractioned and separated	2.5, 5, and 10 mg/kg/day in 0.5% CMC suspension, oral gavage, 45 days	Female Wistar rats, >12 weeks old	• Serum: increased testosterone at all doses; increased estradiol at 10 mg/kg; decreased progesterone at 2.5 and 5 mg/kg	Saeed et al., 2023

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Table 1 (*continued*)

MP/NP Type	MP/NP Size	Dose and duration of exposure	Animal model	Effects on steroid levels or steroidogenic enzymes	References
	with 80, 120 and 400 mesh size sieves				
PVC	100–200 μm Ø	10%, 20% and 30% MP equivalent to 49.25 mg/*L*, 98.5 mg/*L* and 147.8 mg/*L*, respectively; dietary exposure, 60 days	Carp (*Cyprinus carpio*) larvae	• Plasma: increased estradiol in females under all conditions; no change in testosterone in males • Brain: downregulation of CYP19B expression in females	Liu et al., 2023
PVC	Unspecified size; dissolved in saline	1000 mg/kg/day, oral administration, 40 days	Male Wistar rats, 180 g (*~6–7 weeks old*)	• Serum: decreased testosterone	Sadeghi et al., 2020
PVC	Unspecified size; dissolved in distilled water	100 and 500 mg/kg/day, in the diet, 60 days	Male Wistar rats, 13–15 weeks old	• Serum: decreased testosterone at the 500 mg/kg dose • Testis: decreased 3β-HSD and 17β-HSD enzyme activity at the same dose	Archana et al., 2018
PVC	60–250 μm Ø	50 and 500 g/100 kg of food diet, 21 days of ad libitum feeding	Female New Zealand White rabbits, 12 weeks old	• Serum: increased estradiol and no change in progesterone	Papp et al., 2024

Abbreviations: MPs/NPs types: EPS, expanded polystyrene; FPS, fluorescent polystyrene; HDPE, high-density polyethylene; LDPE, low-density polyethylene; PA, polyamide; PE, polyethylene; PEG-b-PLA, poly(ethylene glycol)-*block*-polylactide methyl ether; PES, polyester; PET, polyethylene terephthalate; PMMA, polymethyl methacrylate; PP, polypropylene; PS, polystyrene; PVC, polyvinyl chloride.
Steroidogenic enzymes/proteins: 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 20β-HSD, 20β-hydroxysteroid dehydrogenase; CYP11A, cytochrome P450 family 11 subfamily A (cholesterol side chain cleavage cytochrome P450 or P450scc); CYP11A1, cytochrome P450 family 11 subfamily A, polypeptide 1 (cholesterol side chain cleavage cytochrome P450 or P450 scc); CYP17A1, cytochrome P450, family 17, subfamily a, polypeptide 1 (P450C17 or 17α-hydroxylase); CYP19A1, cytochrome P450, family 19, subfamily a, polypeptide 1 (P450arom or aromatase, mouse and rat); CYP19A1A, cytochrome P450, family 19, subfamily a, polypeptide 1a (P450arom or aromatase, zebrafish); CYP19B, cytochrome P450, family 19 (brain aromatase, carp); Ldlr, low density lipoprotein receptor; Lhcgr, luteinizing hormone/chorionadotropin receptor; Scarb1, scavenger receptor class B, member 1; StAR, Steroidogenic Acute Regulatory protein; Stard5, StAR related lipid transfer domain containing 5.
For each subject tested, the age expressed in weeks and reported in brackets is an estimate based on the information provided in the respective study. Literature search was performed in PubMed; last check was on 31 March 2026.

Indeed, only two studies examined brain steroid levels, reporting increased testosterone in adult female Zebrafish exposed to PS (Adhikari et al., 2024), and decreased progesterone and increased cortisol in the head of the wild wharf roach *Ligia exotica* collected in an area with expanded polystyrene (EPS)-contaminated gravel shore that also contained PA, PP and PS (Choi et al., 2023), suggesting that effects of MPs/NPs contamination might indeed alter neurosteroidogenesis. Many studies have been conducted in fish (a common model organism in toxicological tests) or in rodents, while very few studies examined serum steroid levels in humans, likely due to the difficulty in identifying and discriminating the effects of multiple pollutants and contaminants. A recent study reported that higher amounts of placental MPs/NPs are associated with (i) lower cortisol and cortisone levels in umbilical cord serum, (ii) higher DHEA and androstenedione levels, and (iii) altered cortisol/DHEA and glucocorticoid/androgenic ratios, suggesting putative disruptions in the endocrine homeostasis that may impact fetal development (Liu et al., 2025). A recent study conducted in girls with central precocious puberty reported high serum levels of PE and PVC (among different MPs found in their blood) compared to healthy controls. In these patients, progesterone levels were negatively correlated with total MPs concentration, as well as with PVC content, while DHEA sulfate levels were positively correlated with total MPs concentration, as well as with PE content (Zang et al., 2025). Studies conducted in PVC-exposed workers reported a modest reduction in testosterone levels, compared to unexposed workers, and a negative correlation between free testosterone and urinary plasticizers' metabolites (Metwally et al., 2021; Pan et al., 2006). Elevated serum estradiol levels were also reported in healthy men exposed to di(2-ethylhexyl) phthalate plasticizer (inhaled in PVC production plants), and levels of estradiol and the estradiol/testosterone ratio positively correlated with urinary di (2-ethylhexyl) phthalate metabolites (Fong et al., 2015). Despite the limited sample size in these studies, these findings suggest that MPs/NPs exposure affects neuroactive steroid content in humans.

4.1. *Progestogens*

Almost all studies examining effects of MPs and NPs on this steroid class have focused on circulating progesterone (see Table 1 for details), except for the study conducted in the wharf roach whole head mentioned above, showing decreased progesterone content following exposure to multiple MPs/NPs particles (Choi et al., 2023). For plasma/serum progesterone levels, we found seven observations for a decrease, three for an increase, and four for no change (summarized in Fig. 2). When considering the plastic type, acute exposure to PA particles through inhalation did not alter plasma progesterone in female Sprague-Dawley rats (Cary et al., 2023). Likewise, exposure to PVC did not alter serum progesterone in female rabbits (Papp et al., 2024). Effects of PE by itself on progesterone levels were not examined; however, PEG exposure increased serum progesterone in female Wistar rats (Rollerova et al., 2015). With respect to PS-based MPs/NPs, a dose-dependent effect was observed in juvenile shrimp, where lower doses increased and higher doses decreased serum progesterone (Li et al., 2023). In female mice, the effects on serum progesterone appear to be strain dependent, with an increase in Kunming mice at the higher dose tested (1 mg/kg) (Qiao et al., 2025), a decrease in C57BL/6 J mice (Gholiof et al., 2025), and no change in ICR mice (Dou et al., 2024); no change was also observed in ovarian cell culture medium from CD-1 mice (Alahmadi et al., 2025). In female Sprague-Dawley and Wistar rats, decreased serum progesterone and decreased ovarian expression of steroidogenic enzymes (CYP19A1 and StAR protein) were reported (Amran et al., 2023; Saeed et al., 2023; Valencise et al., 2025a; Wang et al., 2023) (see summary in Fig. 2 and details in Table 1).

To the best of our knowledge, no studies have measured levels of the precursor pregnenolone, its metabolites other than progesterone, or the progesterone metabolites allopregnanolone and pregnanolone following MPs/NPs exposure. Although no direct evidence exists, we could

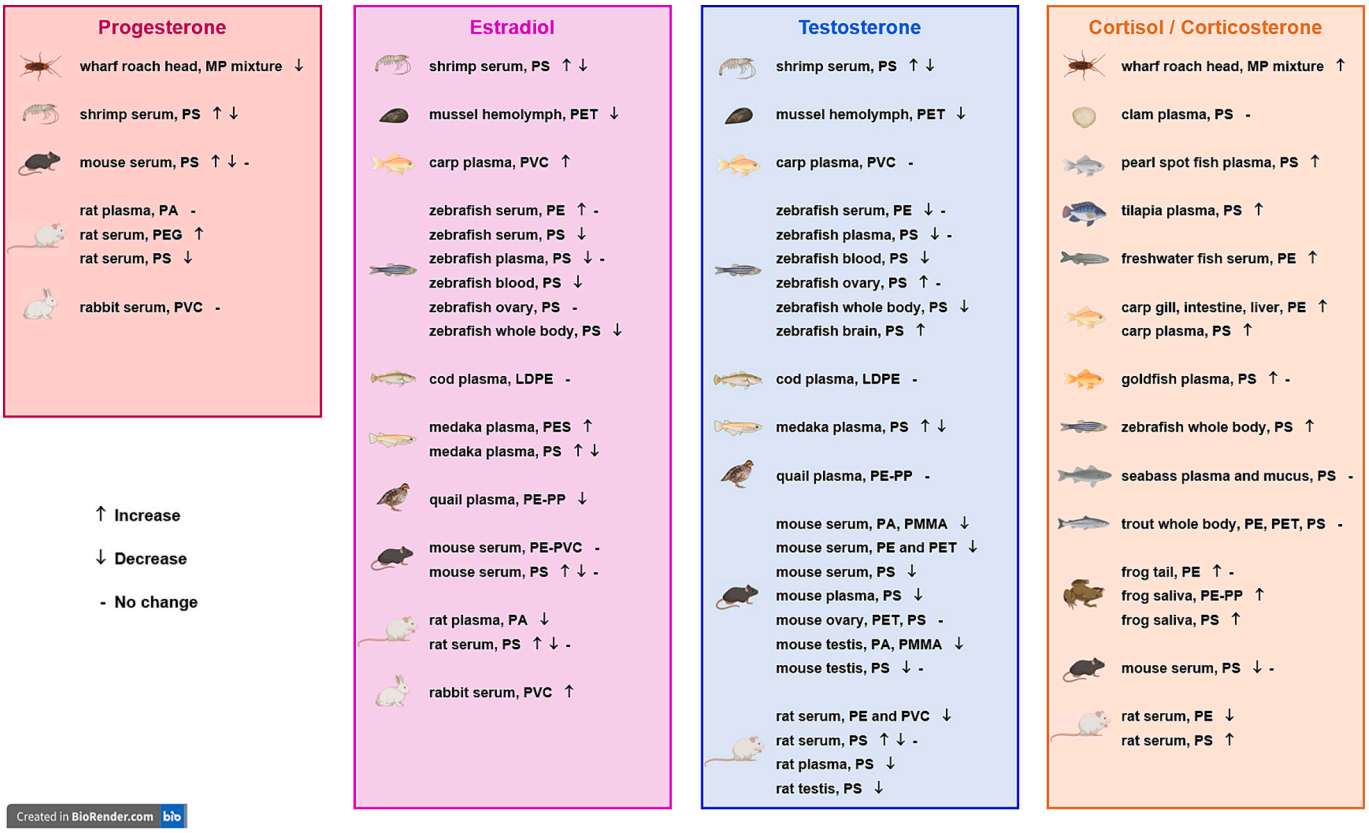

Fig. 2. Diagram summarizing increases (↑), decreases (↓) or no change (—) in progesterone, estradiol, testosterone and cortisol/corticosterone levels following exposure to different MPs/NPs types; details for each study are reported in Table 1. Abbreviations: LDPE, low-density polyethylene; MP, microplastic; PA, polyamide; PE, polyethylene; PEG, poly(ethylene glycol)-*block*-polylactide methyl ether; PES, polyester; PET, polyethylene terephthalate; PMMA, polymethyl methacrylate; PP, polypropylene; PS, polystyrene; PVC, polyvinyl chloride.

reasonably assume that levels of these neuroactive steroids might also be affected by MPs/NPs exposure. In support of this hypothesis, most studies reported a decrease in the expression of several steroidogenic enzymes involved in cholesterol translocation to the inner mitochondrial membrane (StAR), its conversion to pregnenolone (CYP11A), or the conversion of pregnenolone into progesterone (3β-HSD) in ovary, testis or adrenals (see Table 1 for details), suggesting impaired peripheral steroidogenesis. Accordingly, pregnenolone levels were increased in ovarian cell culture medium obtained from PET- and PS-exposed CD-1 mice (Alahmadi et al., 2025). The possibility that a similar effect might occur *in vivo* in brain and other organs cannot be ruled out. Indeed, very few studies investigated the effect of plasticizers and plastic additives on allopregnanolone levels. A decrease in its concentrations has been reported in zebrafish embryos exposed to di(2-ethylhexyl) phthalate (Kang et al., 2025). Moreover, studies in humans examined associations between plastic additives and allopregnanolone levels, with contrasting findings. While bisphenols and phthalates were found not to be associated with allopregnanolone concentrations in postpartum disorders (Jacobson et al., 2021), in women suffering from antepartum depression, elevated levels of bisphenol A were found to be associated with reduced levels of allopregnanolone and DHEA sulfate (Aishwarya et al., 2025), although a causal link between the two remains to be demonstrated.

4.2. Estrogens and androgens

Numerous studies have examined the effects of MPs/NPs on gonadal function, and specifically their detrimental outcome on the ovary and testis. Most of them focused on estradiol and testosterone levels as a proxy for gonadal function and reported decreased levels in serum and/or gonadal tissue. We refer the reader to more focused reviews on this specific topic (Hong et al., 2023; Hu et al., 2024). Here, we focus on those studies reporting multiple hormones' levels, or examining gene expression changes in steroidogenic enzymes, or being performed in rodents. Details are reported in Table 1.

The majority of these studies examined serum, plasma or hemolymph levels of estradiol and/or testosterone, with very few exceptions. One study reported decreased whole body levels of estradiol and testosterone in adult female zebrafish exposed to PS for 28 days (Mohammadzadeh et al., 2024), while another one reported increased testosterone levels in the brain and ovary of adult female zebrafish exposed to PS for 21 days, along with altered ovarian gene expression of steroidogenic enzymes and decreased serum estradiol (Adhikari et al., 2024). With respect to peripheral levels, estradiol and testosterone levels were decreased in the hemolymph of wild Mediterranean mussels (*Mytilus galloprovincialis*) following 32-day PET exposure (Choi et al., 2022). A dose-dependent effect was observed in juvenile shrimp exposed to PS for 28 days, where lower doses increased and higher doses decreased serum estradiol and testosterone (Li et al., 2023). In adult medaka fish (*Oryzias latipes*), plasma estradiol increased in males at day 3 of PES exposure (Kim et al., 2023b); similarly, after 60 days of PS exposure, both plasma estradiol and testosterone were increased in males, but were decreased in females (Wang et al., 2019). In adult male and female zebrafish, PS exposure either decreased or did not alter estradiol and testosterone (Adhikari et al., 2025; Chen et al., 2025; Lin et al., 2023; Ye et al., 2024). Importantly, in zebrafish, intergenerational effects of MPs/NPs exposure on steroidogenesis were also described, with increased serum estradiol in males (with no change in females), and decreased serum testosterone and 11-ketotestosterone in females (with no change in males) whose parents were exposed to PE for

35 days before mating (Xue et al., 2024a). Moreover, LDPE exposure did not change plasma levels of estradiol, testosterone and 11-ketotestosterone in male and female Atlantic cod (*Gadus morhua*) (Fernández-Míguez et al., 2023), while 60-days PVC exposure increased plasma estradiol in female carp (*Cyprinus carpio*) larvae, but did not change testosterone in males (Liu et al., 2023). Exposure to a PE-PP mixture also decreased plasma estradiol in female Japanese quail (*Coturnix japonica*) but did not change testosterone in males (Monclús et al., 2022).

In mammals, differential effects of MPs/NPs on peripheral estradiol and testosterone levels were described (see Table 1 for details of each study). PA and PMMA exposure for 28 days decreased serum and testis testosterone levels in young adult male ICR mice (Zhang et al., 2024b), while acute exposure to PA particles through inhalation decreased plasma estradiol in female Sprague-Dawley rats (Cary et al., 2023). PE exposure decreased serum testosterone in C57BL/6 J mice (Wang et al., 2026) as well as Albino and Wistar rats (Ijaz et al., 2024; Ijaz et al., 2023b; Kehinde et al., 2024; Kehinde et al., 2026); likewise, long-term (29 weeks starting from adolescence) PET exposure decreased serum testosterone in adult male C57BL/6 N mice (Jeong et al., 2025). However, a PE-PVC mixture did not change serum estradiol in juvenile female C57BL/6 J mice (Zang et al., 2025). PS exposure decreased serum or plasma testosterone in several common laboratory strains of adult male mice (Cai et al., 2023; Feng et al., 2025; Fu et al., 2023; Jin et al., 2024; Li et al., 2024b; Liu et al., 2026; Liu et al., 2024; Nikolic et al., 2022; Qu et al., 2024; Sui et al., 2023; Wei et al., 2022; Wu et al., 2026; Zangene et al., 2024; Zhang et al., 2023; Zhao et al., 2025a; Zhao et al., 2025b), and rats (Akbar and Ijaz, 2024; Alsenousy et al., 2026; Ebrahim et al., 2024; Hamza et al., 2023; Hwang et al., 2024; Ijaz et al., 2023a; Rizwan et al., 2023; Setiyowati et al., 2026; Wang et al., 2024). Interestingly, testosterone levels were reduced in male offspring of ICR mice (Dou et al., 2024; Zhao et al., 2023), and Sprague-Dawley rats (Jiang et al., 2026) exposed to PS during gestation, suggesting a possible intergenerational effect of MPs/NPs exposure on steroidogenesis. PS also decreased serum estradiol in female mice, specifically the juvenile Kunming (Xue et al., 2024b), the adult ICR (Hu et al., 2026) and the adult C57BL/6 strains (Wei et al., 2022) [although no change in this strain was also reported (Gholiof et al., 2025; Li et al., 2026)], as well as in adult female Sprague-Dawley (Amran et al., 2023; Wang et al., 2023) and Wistar (Haddadi et al., 2022) rats. However, following PS exposure, serum testosterone was also reported to be increased in male (Lu et al., 2025) and female (Wei et al., 2022) C57BL/6 mice, as well as in female Wistar rats that also had elevated estradiol levels (Saeed et al., 2023), highlighting a wide heterogeneity of effects on sex steroids levels following PS exposure. Indeed, serum estradiol was also increased in adult male BALB/c (Zhao et al., 2025b), adult female (Yang et al., 2022) and male (Wei et al., 2022) C57BL/6 mice, as well as early pregnant Kunming mice (Qiao et al., 2025) all exposed to PS, while in female ICR (Dou et al., 2024) and in male C57BL/6 mice (Yang et al., 2022) it did not change. Likewise, no change in plasma testosterone (Valencise et al., 2025b) or estradiol (Valencise et al., 2025a) was reported in male and female Wistar rats, respectively. Finally, PVC exposure decreased serum testosterone in adult male Wistar rats (Archana et al., 2018; Sadeghi et al., 2020), while it increased estradiol in female rabbits (Papp et al., 2024). To summarize, MPs/NPs exposure decreases estradiol and testosterone peripheral levels in most of the studies; however, elevations in their levels have also been reported, so no clear conclusions on their effects on steroidogenesis can be drawn at the moment. Furthermore, no studies have yet examined effects of MPs/NPs on levels of other key androgen neuroactive steroids.

4.3. Corticosteroids

We identified 22 studies measuring effects of MPs/NPs on cortisol/corticosterone levels in serum, plasma, saliva, tail, gill, intestine, liver or whole body, mostly focused on aquatic organisms (see Table 1 for details). Only one study reported increased cortisol levels in the whole head of the wharf roach *Ligia exotica* exposed to several MPs types from the polluted environment (Choi et al., 2023), indicative of putative changes of this hormone in the brain. Exposure to PE particles increased cortisol in serum of freshwater fish (*Tor putitora*) (Ullah et al., 2026), and in gill, intestine and liver of carp (*Carassius carassius*) (Yu et al., 2026), while in the tail of *Xenopus laevis* frog larvae either an increase or no change were reported (Martin et al., 2025; Ruthsatz et al., 2023). Likewise, increased corticosterone was also reported in saliva of juvenile wrinkled frogs (*Glandirana rugusa*) exposed to 60 mg/L of PE and PP for 6 weeks (Park and Do, 2025). By contrast, male Sprague-Dawley rats exposed to PE (3.75, 15, or 60 mg/kg for 35 days) showed decreased serum cortisol, albeit associated to a paradoxical increase in serum ACTH levels (Farag et al., 2024). This ACTH-cortisol dissociation, accompanied by an adrenal gland enlargement, suggests that PE may impair adrenal responsiveness to ACTH or may disrupt the HPA axis regulatory feedback. In another model, sea trout (*Salmo trutta*) embryos were exposed to different MPs/NPs (PE, PET and PS, for 113 days), and a tendency for increased whole-body corticosterone, dehydrocorticosterone and cortisone levels was observed, although none of these changes resulted statistically significant, while detectable cortisol concentrations were found only in PS-exposed fish larvae (Jakubowska et al., 2020). Following PS exposure, no change in cortisol levels was observed in plasma from adult clams (*Telligarca granosa*) exposed to PS for 14 days (Shi et al., 2020), in plasma and mucus from juvenile seabass (*Dicentrarchus labrax*) following 96 h exposure (Brandts et al., 2021), or in plasma from adult goldfish (*Carassius auratus*) following 30 days exposure (Brandts et al., 2022). However, in this latest species, increased plasma cortisol has also been reported, with a peak observed at 72 h exposure (Kim et al., 2023a). Indeed, following PS exposure, a dose-dependent increase in cortisol was observed in several species and conditions, including i) whole body levels in adult zebrafish exposed to PS for 28 (Mohammadzadeh et al., 2024) or 30 days (Ahmadifar et al., 2024), and in zebrafish larvae exposed to PS for 2 days only (Brun et al., 2019), as well as ii) plasma levels in juvenile pearl spot (*Etroplus suratensis*) (Das et al., 2025), juvenile silver carp (*Hypophthalmichthys molitrix*) (Zaman et al., 2024), and Nile tilapia (*Oreochromis niloticus*) (Das et al., 2023) all exposed for approximately 2 weeks. Moreover, a trend for increased saliva corticosterone levels was reported in juvenile male and female pond frogs (*Pelophylax nigromaculatus*), following 6 weeks of PS exposure (Park et al., 2024). Finally, three studies examined the effects of PS exposure in mammals; no change in serum corticosterone was observed in female Swiss mice following 21 days exposure (Barichello et al., 2025), while a decrease in serum corticosterone was observed in male mice (unspecified strain and age) following 4 weeks exposure, an effect also associated with decreased adrenal expression of StAR, P450scc and 3β-HSD (Xiong et al., 2025). By contrast, Babaei and collaborators investigated the impact of PS in adult male Wistar rats exposed for 35 days, reporting a dose-dependent increase in serum cortisol that was correlated with metabolic alterations, including increased blood glucose, likely due to stress-induced gluconeogenesis (Babaei et al., 2022).

To summarize, the majority of the studies report an increase in cortisol/corticosterone levels suggesting that exposure to MPs/NPs acts as a stressor, stimulating HPA axis activation. However, one study in the wharf roach brain and two studies in mammals (mice and rats) report decreased cortisol/corticosterone levels following exposure to different MPs/NPs types, suggesting that such exposure may disrupt the physiological homeostasis of the HPA axis. Additional studies are required to further dissect the effects of MPs/NPs on corticosteroids, HPA axis function, sensitivity to stress and their relevance for stress-related neuropsychiatric diseases.

5. Conclusions and future perspectives

Neuroactive steroids affect several brain functions, including neuronal excitability, neuroplasticity, neuroimmunity,

neurodevelopment, sexual dimorphism, cognition, mood, reward, stress homeostasis. As such, changes in neuroactive steroid levels are relevant for several neuropsychiatric, neurological and neurodegenerative diseases. Worryingly, steroidogenesis can be altered in different species exposed to several types of MPs/NPs. It is well known that MPs/NPs exposure affects reproductive function; as such, the most studied steroid hormones are the gonadal steroids estradiol and testosterone, mainly examined in aquatic organisms, the most common animal models in toxicology. However, in the last five years, studies on putative toxic effects of MPs/NPs in mammals have increased. Among the 75 papers screened for effects of MPs/NPs on steroid levels (see Table 1), 46 are in mammals, mainly mice and rats, with most of them reporting altered levels of peripheral progesterone, estradiol, testosterone or corticosterone/cortisol. Only one study reports altered levels of progesterone and corticosterone in the whole head of the wharf roach, suggesting that MPs/NPs may also affect neurosteroidogenesis. Given that MPs/NPs accumulate in the human brain (Nihart et al., 2025), it is likely that they may directly affect brain function, including neurosteroidogenesis. Indeed, MPs/NPs can reach the brain through multiple routes; during development, an immature blood-brain barrier (BBB) allows penetration of MPs/NPs from the placenta to the brain (Zhang et al., 2024a), while in adulthood they may access the brain either by crossing a compromised BBB, or bypassing it through the olfactory route after inhalation (Baroni et al., 2025; Gettings et al., 2026). *In vitro* and *in vivo* studies showed that MPs/NPs can passively penetrate the BBB due to their high hydrophobicity (Ianos et al., 2026), and they can disrupt BBB integrity by impairing endothelial function, reducing tight-junction proteins and promoting oxidative stress and inflammation (Baroni et al., 2025; Gettings et al., 2026). Once inside the brain, MPs/NPs induce oxidative stress and mitochondrial dysfunction in neurons and glial cells, thus promoting the release of pro-inflammatory cytokines (Baroni et al., 2025; Gettings et al., 2026). These phenomena have been associated with impaired neurosteroidogenesis (Yilmaz et al., 2019). Moreover, MPs/NPs have been shown to alter the expression of steroidogenic enzymes in the gonads (see Table 1 for references); thus, it is likely that a similar mechanism might also occur in brain. Yet, direct evidence for significant alterations induced by MPs/NPs in the brain levels of the steroid precursor pregnenolone and its neuroactive metabolites, including allopregnanolone, DHEA, or androstanediols, is still virtually absent.

Other challenges still need to be tackled. Whether the effect of MPs/NPs on altered steroidogenesis is reversible or not remains another open question. Moreover, some studies reported decreased testosterone levels in male offspring of mice exposed during pregnancy (Dou et al., 2024; Zhao et al., 2023); therefore, examining long-term and putative intergenerational effects of MPs/NPs on steroidogenesis is key for the offspring health. Dissecting the impact of specific plastic types is also important to better tailor plastic products on those less dangerous polymers for human and animal health. Plastic contamination is a rapidly growing issue worldwide. Thus, investigating the impact of MPs/NPs on neurosteroidogenesis is key to our understanding of how MPs/NPs impact those physiological processes influenced by steroidogenesis (i.e. the stress response, puberty, the ovarian cycle, pregnancy, menopause, aging), whose alterations may contribute to psychiatric, neurological and neurodegenerative diseases.

Author confirmation statement

The manuscript has been read and approved by all authors.

CRediT authorship contribution statement

Patrizia Porcu: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Mariangela Serra:** Writing – review & editing, Writing – original draft. **Augusta Pisanu:** Writing – review & editing. **Maria Giuseppina Pisu:** Writing – review & editing. **Liana Fattore:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization.

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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.

Data availability

No data was used for the research described in the article.

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