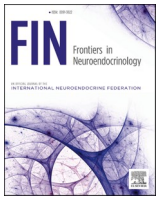
Frontiers in Neuroendocrinology 76 (2025) 101160

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne



Review article

Progestagens and progesterone receptor modulation: Effects on the brain, mood, stress, and cognition in females

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ARTICLE INFO

Keywords:
Cognition
Brain
Females
Mood
Progesterone
Progestins
Progestagens
Stress

ABSTRACT

Progesterone is a highly lipophilic gonadal hormone that can influence behavior and mental health through its receptors in the brain. Fluctuations in progesterone levels across critical periods of a females life are associated with increased susceptibility to mental conditions.

This review highlights the effects of progestagens, including progesterone and synthetic progestins, on the brain, mood, stress, and cognition in females. The primary focus is on experimental pharmacological research that teases out the distinct effects of progestagens from those of estrogens. Additionally, the key literature on puberty, the menstrual cycle, pregnancy, perimenopause, hormonal contraceptives, and menopausal hormone therapy is reviewed, although conclusions are limited by the nested effects of progestagens and estrogens.

Single study-findings suggest an influence of progesterone on amygdala reactivity related to processing of emotional stimuli and memory. In patients with premenstrual dysphoric disorder, progesterone receptor modulation improves premenstrual mood symptoms and potentially enhances fronto-cingulate control over emotion processing. The interaction between progestagens and the systems involved in the regulation of stress seems to influence subjective experiences of mood and stress. Sparse studies investigating the effects of progestin-only contraceptives suggest effects of progestagens on the brain, mood, and stress. Progesterone and progestins used for contraception can influence neural processes as myelination and neuroprotection, exerting protective effects against stroke. Concerning menopausal hormonal therapy, the effects of progestins are largely unknown.

Levels of progesterone as well as type, administration route, timing, dose regimen, metabolism, and intracellular activity of progestins in hormonal contraceptives and menopausal hormonal therapy are factors whose effects remain to be elucidated. Altogether, current knowledge highlights the potential role of progestagens in females health but also calls for well-designed pharmaco-behavioral studies disentangling the effects of progestagens from those of estrogens.

1. Introduction

Progestagens, including progesterone and synthetic progestins,

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https://doi.org/10.1016/j.yfrne.2024.101160
Received 19 August 2024; Received in revised form 28 October 2024; Accepted 4 November 2024
Available online 6 November 2024

Abbreviations

ALLO	Allopregnanolone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANS	Autonomic nervous system
BDNF	Brain-derived neurotrophic factor
cPRs	Classical intracellular progesterone receptor
dACC	Dorsal anterior cingulate cortex
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
HC	Hormonal contraception
HCs	Hormonal contraceptives
HPA axis	Hypothalamic-pituitary-adrenal axis
HPG axis	Hypothalamic-pituitary–gonadal axis
HT	Hormone therapy
IUD	Intrauterine device
JAK	Janus kinase
LH	Luteinizing hormone
MAPK	Mitogen-activated protein kinase
MAPR	Membrane-associated progesterone receptor
MCAO	Middle cerebral occlusion
MPA	Medroxyprogesterone acetate
mPRs	Membrane progesterone receptor
mRNA	Messenger ribonucleic acid
NETA	Norethisterone acetate
NMDA	N-methyl-D-aspartate
PGRMC	Progesterone receptor membrane component
PI3K	Phosphatidylinositol 3-kinase
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
PND	Perinatal depression
PR	Progesterone receptor
SPRM	Selective progesterone receptor modulator
STAT	Signal transducer and activator of transcription
UPA	Ulipristal acetate

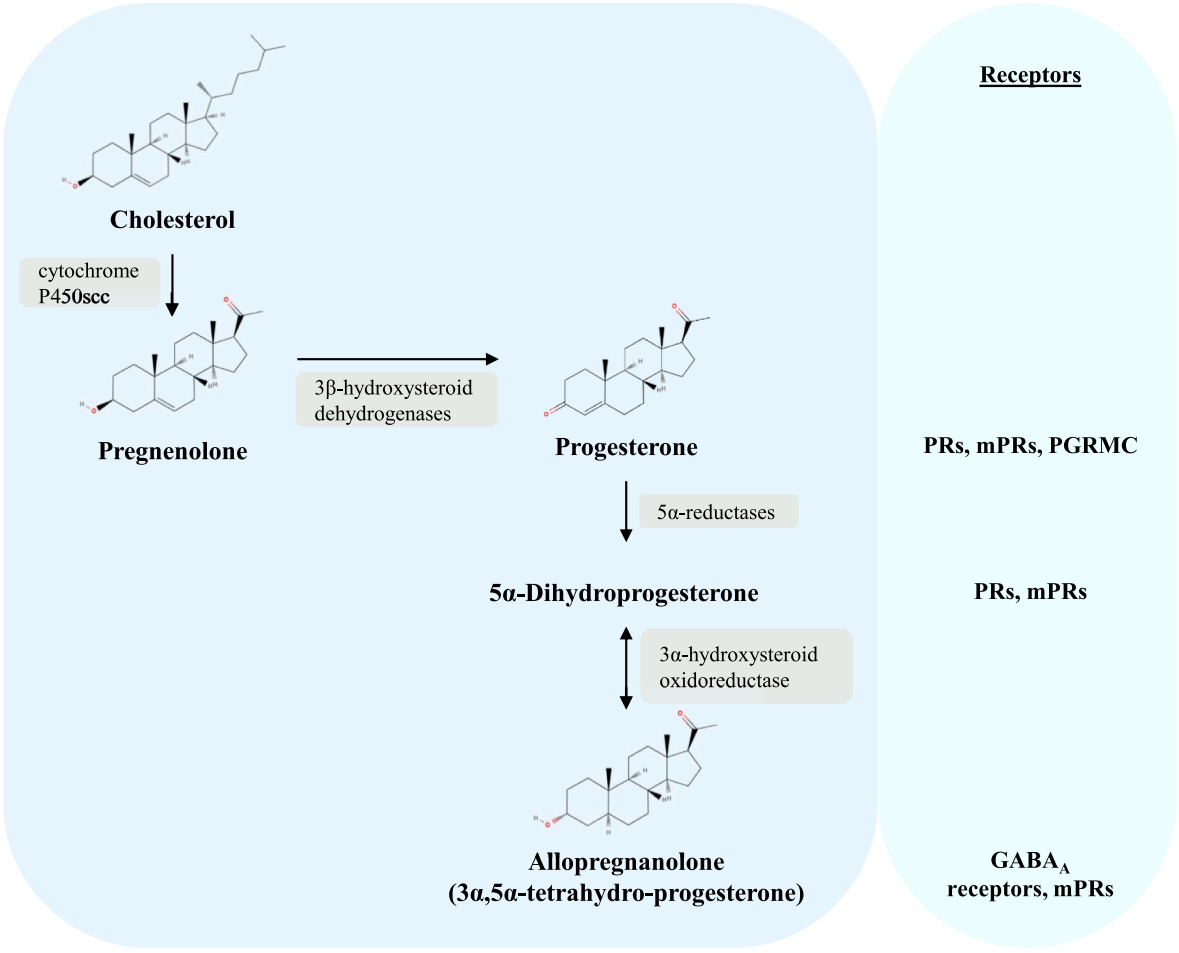

Fig. 1. Schematic overview of the Pregnenolone-Progesterone-Allopregnanolone pathway and main receptors involved in their actions in brain. Progesterone synthesis requires the conversion of cholesterol inside the mitochondrion by the cytochrome P450 side-chain cleavage enzyme (P450scc) to pregnenolone and then the conversion of pregnenolone to progesterone by the 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerases (3β-HSD). Progesterone can be metabolized into 5α-dihydroprogesterone by the steroid 5α-reductases, and then to allopregnanolone (ALLO) also named 3α,5α-tetra-hydroprogesterone by the 3α-hydroxysteroid oxidoreductase (3α-HSOR). Progesterone can bind to multiple receptors including the classical intracellular receptors (PR) the membrane receptors (mPRs) and the membrane binding sites (PGRMC1). 5α-dihydroprogesterone binds to the classical receptors PR and has relatively high binding affinity for mPRα. ALLO has no affinity for the intracellular PR, but is a potent allosteric modulator of $GABA_A$ receptors. Some neuroprotective effects of allopregnanolone may be mediated by the membrane progesterone receptor mPRδ. PRs = Progesterone Receptors, mPRs = Membrane Progesterone Receptors Receptors, PGRMC = Progesterone Receptor Membrane Component, $GABA_A$ = Gamma-Aminobutyric Acid type A, HC = Hormonal Contraception, HT = Hormone Therapy.

constitute one of the three classes of sex steroids, along with estrogens and androgens (Plant & Zeleznik, 2014). Sex steroids are part of the broader steroid hormone family that also includes corticosteroids, namely glucocorticoids and mineralocorticoids, as well as vitamin D (Monastra et al., 2018; Plant & Zeleznik, 2014). Progesterone is the key steroidogenic precursor for the synthesis of estrogens, and androgens, as well as glucocorticoids and mineralocorticoids. Following its synthesis by the ovaries, placenta, and adrenal glands in females, progesterone can easily pass through the blood–brain barrier because of its high lipophilicity, and can therefore accumulate in the brain (Bixo et al., 1997; Bixo et al., 1986). As a neurosteroid, it is synthesized locally within the nervous system (Guennoun 2020). Progesterone exerts its functions by acting on its receptors (Barth et al., 2015; Brinton et al., 2008; Mani, 2006) that are expressed in brain areas relevant to cognitive and affective processes. Furthermore, progestagens can influence the activity of the hypothalamic–pituitary–gonadal (HPG) axis through feedback mechanisms and modulation of upstream HPG components (Giatti et al., 2016; Griksiene et al., 2022; Phumsatitpong et al., 2021) such as the negative feedback exerted on the hypothalamus and pituitary gland, by inhibiting the secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH).

Some effects of progesterone may be mediated by its neuroactive metabolite allopregnanolone (ALLO), also known as 3α5α-tetrahydroprogesterone. A schematic overview of the Pregnenolone-Progesterone-Allopregnanolone pathway and main receptors involved in their actions in brain is provided in Fig. 1 (for a review on progesterone biosynthetic and metabolic pathways and enzyme distribution in brain and spinal cord, see Guennoun, 2020; Guennoun et al., 2015). On the other hand, synthetic progestins, administered in the form of hormonal contraception (HC) or menopausal hormone therapy (MHT) differ in their chemical structure and binding properties. Table 1 lists commonly used synthetic progestins in HC and MHT.

In males, progesterone levels are relatively stable throughout fertile age (Oettel & Mukhopadhyay, 2004), but they significantly fluctuate in females during critical windows of their reproductive life, i.e., puberty, menstrual cycle, pregnancy and postpartum, perimenopause and even during HC use (Fig. 2; Carlson & Shaw, 2019; Stein et al., 2014; Sundstrom-Poromaa et al., 2020). This review will particularly focus on research on females. Notably, for some, these reproductive transition periods can be associated with affective and cognitive symptoms of varying severity (e.g., premenstrual dysphoric disorder (PMDD), perinatal depression (PND; including postpartum depression) or perimenopausal depression) (Epperson et al., 2012; Hantsoo et al., 2022; Association, 2013). According to the hormone sensitivity hypothesis, the underlying cause may be an increased sensitivity to physiological reproductive hormone fluctuations, as these disorders have not been associated with altered levels of progesterone and/or estradiol (Pope et al., 2017; Schiller et al., 2015; Schweizer-Schubert et al., 2021; Skalkidou et al., 2012). Such hormonal changes have indeed the potential to modulate neurophysiological and behavioral dynamics (e.g., emotion regulation), which is of relevance also to the general field of psychiatry, as it has been shown that the disproportionate sex-specific prevalence of mental conditions that are more common in females is associated with hormonal transition phases (Bale and Epperson, 2015, 2017; Shansky and Murphy, 2021).

This review extends beyond the role of progesterone in reproduction, which includes the preparation of the lining of the uterus for a potential pregnancy and, if fertilization occurs, its maintenance to support the developing embryo. Instead, current knowledge on the effects of progesterone on the brain, mood, stress, and cognition is presented, together with insights from preclinical evidence and findings on progestins. *A particular focus of this review is on experimental pharmacological studies that specifically target endogenous or exogenous progestagens in relation to the brain, mood, stress, and cognition.* In addition, we provide overviews of key literature and reviews or *meta*-analyses of studies on the menstrual cycle, pregnancy, postpartum, menopausal transition, HC, and MHT. Importantly, in these studies, the specific effects of progestagens cannot be disentangled from the effects of estrogens.

Table 1
Progestins commonly used in hormonal contraception (HC) and menopausal hormone therapy (HT).

Synthetic Progestin	HC	MHT
Drospirenone[a,b]	x	x
Levonorgestrel[a,b,c]	x	x
Desogestrel[a,b]	x	
Dienogest[a,b]	x	
Norethindrone[a,b]	x	
Gestodene[b]	x	
Norgestimate[b]	x	x
Etonogestrel[d]	x	
Medroxyprogesterone acetate[b,e]	x	x

[a] Used in progestin-only pills.
[b] Used in combined oral contraceptives.
[c] Used in intrauterine devices.
[d] Used in contraceptive implants and vaginal rings.
[e] Used in injections.

2. Progesterone across the female lifespan – from puberty to menopause

The female reproductive lifespan is characterized by significant fluctuations in progesterone. Estradiol levels increase until menarche, while progesterone does not increase until the first ovulation, which may not coincide with menarche as the first menstrual cycles may be anovulatory (Fig. 2A). During the follicular phase of the menstrual cycle, progesterone levels remain low when estradiol alone rises. Upon ovulation, the corpus luteum forms from the remains of the leading follicle, which undergoes luteinization and continues to produce sex hormones, predominantly progesterone, leading to an increase in hormone levels. During the mid-luteal phase, progesterone reaches its maximum, and estradiol levels reach a secondary peak. Thereafter, both progesterone and estradiol levels decrease rapidly to their lowest levels during the late luteal phase until the onset of the next menstruation (Rehbein et al., 2021; Schmalenberger et al, 2021; see Fig. 2B for the progesterone profile).

Upon ovulation, if an oocyte becomes fertilized and pregnancy occurs, progesterone levels continue to rise to levels approximately ten times the mid-luteal levels, peaking at term pregnancy, before rapidly returning to follicular-phase levels within 24–28 h after delivery (Löfgren & Bäckström, 1990; Sundstrom-Poromaa et al., 2020; see Fig. 2D). The reproductive lifespan ends with the cessation of menstrual periods, with fluctuating and decreasing levels during perimenopause and finally stable low levels of progesterone during postmenopause (Stein et al., 2014; Fig. 2E).

3. Synthetic progestagens

Synthetic progestagens, also known as progestins, were first developed in the 1930s with the aim of controlling ovulation and treating menstrual disorders such as irregular menstruation, amenorrhea, and premenstrual syndrome (García-Sáenz et al., 2023). After the introduction of “the pill” in the 1960 s, which was a pivotal feminist milestone and paved the way for female sexual self-determination, the use of synthetic progestins (and estrogens) became widespread (Petitti & Sidney, 2005). Progestins are derived from plant sources, such as yams or soybeans, or are fully synthesized in the laboratory and are available in various forms that differ in their chemical structure and affinity for estrogen, progesterone, androgen, glucocorticoid, and mineralocorticoid receptors (Africander et al., 2011; Bitzer & Simon, 2011; Enfield et al., 2020). They can be clustered into progestins structurally related to

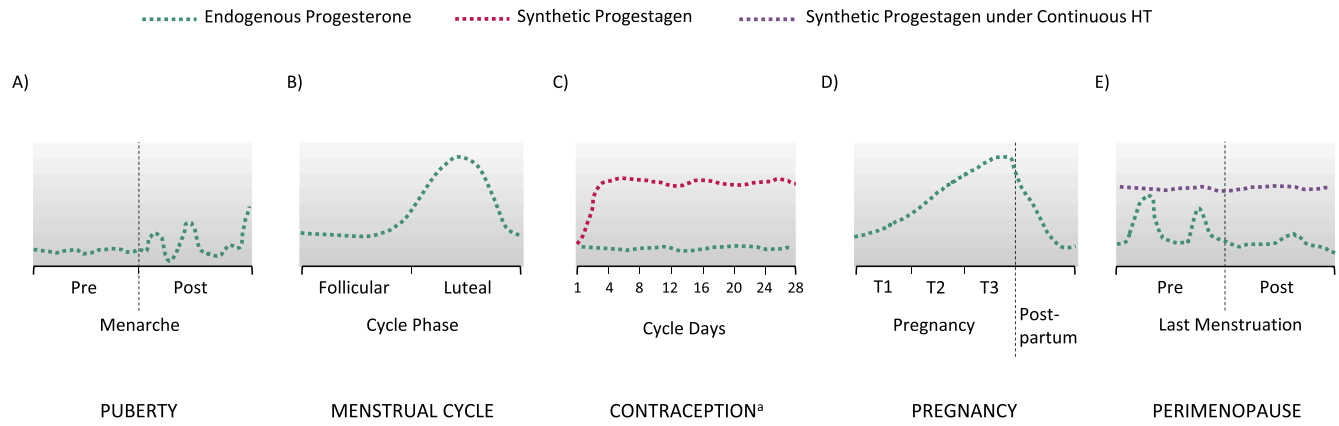

Fig. 2. Endogenous and synthetic progestagen levels across the female reproductive lifespan, including the time windows of A) puberty, B) the menstrual cycle, C) hormonal contraception use, D) pregnancy, and E) perimenopause. T1 = trimester 1 (1–12 weeks), T2 = trimester 2 (13–27 weeks), T3 = trimester 3 (28–40 weeks), HT = hormone therapy. [a] The profile of the depicted synthetic progestagens represents an example for Oral Contraception.

progesterone (pregnane derivatives and 19-norpregnane derivatives), those related to testosterone (ethinylated estranes and 13-ethylgonanes, and the non-ethinylated dienogest), and the spironolactone derivative drospirenone (Stanczyk et al., 2024). Currently, progestins are used in both HC and MHT, as exemplified in Table 1.

HC is still one of the most reliable birth control methods and is used by millions of adolescents and adults worldwide. According to a recent report of the United Nations, worldwide around 26 % of women of reproductive age (15 – 49 years) currently use hormonal oral contraceptives, injectable, or implants (247 million people) and additionally around 17 % (161 million) use intrauterine devices (IUDs, hormonal or copper) (United Nations, 2022). HC has evolved further since its introduction, with a wide variety of formulations and administration methods currently commercially available, each containing one out of approximately nine different progestins (Griksiene et al., 2022; Table 1). Some contraceptives contain both a progestin and an estrogen component (combined HCs), whereas others contain only progestin. HCs are available in various forms, including pills, patches, injectables, implants, and intrauterine devices (IUDs), and are typically prescribed in a cyclical (e.g., combined oral contraceptives ("the pill" or COCs), patches) or long-lasting/continuous (e.g., implants, IUDs) regimen. Through the administration of synthetic sex steroids, HCs affect estradiol, progesterone, and testosterone levels; and the majority of HCs nowadays suppresses ovulation (Fig. 2C; Lewis et al., 2019).

In MHT, progestagens are used alongside estrogens (and androgens) to alleviate symptoms associated with hormonal deficiencies, particularly those occurring during perimenopause. In MHT, progestagens protect the endometrium from estrogen-induced hyperplasia and potential malignancy (Stanczyk et al., 2013). The administered progestagens include natural progesterone, dydrogesterone, and a range of synthetic progestins (e.g., medroxyprogesterone acetate, norethindrone, levonorgestrel; Table 1). MHT is also available in various forms, including tablets, patches, pessaries, and gels, and is typically prescribed in a cyclical or continuous regimen on the basis of individual needs (Stevenson et al., 2020). Besides their usage in (peri)menopause, vaginally administered progestagens (e.g., utrogestan pessaries) may also provide hormonal support in *in vitro* fertilization and pregnancy (Child et al., 2018).

4. Progesterone receptors and their distribution in the brain

The brain's response to progesterone involves a complex interplay of classical intracellular progesterone receptors (cPRs), membrane progesterone receptors (mPRs), and/or progesterone receptor membrane components (PGRMCs) (Griksiene et al., 2022; Fig. 1). This intricate system is widely distributed throughout the brains of vertebrates, with varying expression levels depending on the brain region, cell type, sex, and hormonal status (Brinton et al., 2008; Guerra-Araiza et al., 2002; Kato et al., 1994; Pang et al., 2013; Petersen et al., 2013; Schumacher et al., 2014).

cPRs primarily act as ligand-activated transcription factors and mediate slow, longer-lasting effects. cPRs undergo conformational modifications upon ligand binding and interact with coactivators to regulate the expression of target genes and protein synthesis (Brinton et al., 2008). In addition, cPRs can be membrane-associated and exert rapid responses by interacting with intracellular signaling pathways, mainly kinases (e.g., phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK; Schumacher et al., 2014). cPRs are classified into two primary isoforms, cPR-A and cPR-B, which result from alternative promoters and translation initiation sites of the same gene. PR-A and −B isoforms regulate a suite of genes that are unique to each isoform, with cPR-B regulating the expression of many more genes than cPR-A does. These isoforms also share the regulation of a subset of genes and for some genes, they exert opposite effects (Azeez et al., 2021; Brinton et al., 2008; Kato et al., 1994; Richer et al., 2002; Schumacher et al., 2014).

mPRs possess seven transmembrane domains and are characterized as G protein-coupled receptors that exist in five isoforms: mPRα, mPRβ, mPRγ, mPRδ, and mPRε (Azeez et al., 2021; Guennoun, 2020; Petersen et al., 2013). PGRMC receptors (PGRMC1/2), initially named 25-Dx, are members of the membrane-associated progesterone receptor (MAPR) family. These receptors activate the JAK/STAT and Src pathways and protein kinase G (Guennoun, 2020), which are not confined to a specific location or type of cell, are widely distributed, and are involved in various physiological and pathological processes (Azeez et al., 2021).

With respect to progesterone receptors in rodents, cPRs are expressed in many brain areas, such as the amygdala, hippocampus, thalamus, frontal cortex, cerebellum, hypothalamus, nucleus tractus solitarius, and bed nucleus of the stria terminalis, (for review, see Brinton et al., 2008; Kato et al., 1994; Schumacher et al., 2014). In the hippocampus, cPRs are expressed throughout the entire neuron, including the cell soma, axons, dendrites, and synapses (Kapur & Joshi, 2021; Schumacher et al., 2014). Although PR-A and PR-B isoforms have been detected in various brain regions, including areas implicated in reproductive behavior, mood regulation, and cognitive function (hypothalamus, hippocampus, prefrontal cortex; Brinton et al., 2008), the exact function of PR-A and PR-B across different brain regions remain understudied (Kapur & Joshi, 2021; Schumacher et al., 2014). The messenger ribonucleic acid (mRNA) expression of five mPR molecules has been demonstrated in the rodent cortex, thalamus, hypothalamus, and mesencephalon (Pang et al., 2013; Zhu et al., 2003). In the rat brain, PGRMC1 protein is found in the hypothalamus, circumventricular organs, ependymal cells of the

ventricular walls, and the meninges (Meffre et al., 2005). *PGRMC1/2*-encoding mRNAs have been found in discrete neuroendocrine nuclei and in the hippocampal, cortical, and cerebellar regions (Intlekofer & Petersen, 2011; Petersen et al., 2013).

The mPRs play essential roles in mediating the effects of progestagens in the brain, such as lordosis behavior, neuroprotection, respiratory control of apnea, olfactory responses to pheromones, and peripheral nerve regeneration (Thomas et al., 2022). In the brain, PGRMC signaling pathways have been suggested to be involved in the control of gonadotropin-releasing hormone (GnRH)/LH release, feminine mating behaviors, fluid balance, neuroprotection and seizure activity (Guennoun et al., 2008; Petersen et al., 2013).

Regarding their distribution in the human brain, the expression of cPR mRNA in the pituitary gland is greater than that of other types of PRs. However, throughout the central nervous system (neocortex, amygdala, hippocampus, nucleus accumbens, thalamus, hypothalamus, caudate, putamen, substantia nigra, medulla, pons, and spinal cord), the expression of different subtypes of mPRs seems to be greater than that of cPRs (Pang et al., 2013). Among the mPRs, the expression of mPRδ is the highest in most human brain areas. Interestingly, mPRδ showed the highest affinity not only for progesterone but also for its metabolite ALLO (Pang et al., 2013).

Progesterone and several of its metabolites including 3α-OH-progesterone metabolites (e.g., ALLO, pregnanolone) can act as modulators of neurotransmitters such as gamma-aminobutyric acid (GABA) (Barth et al., 2015; Giatti et al., 2020; Giatti et al., 2022; Schumacher et al., 2007; González et al., 2020, Steckelbroeck et al., 2004). Progesterone appears to shift the excitatory/inhibitory balance in the brain toward inhibition by decreasing glutamate signaling (Cyr et al.,2001; Foy et al., 2008; Yang et al., 2017) but, more consistently, by increasing GABAergic signaling (e.g., Kaura et al., 2007; Piekarski et al., 2017; Rhodes et al., 2005; Shen et al., 2005). These changes are not the result of a change in neurotransmitter levels (Luine et al., 2017) but rather occur in response to actions on N-methyl-D-aspartate (NMDA) and $GABA_A$ receptors, respectively. While the progesterone metabolite ALLO is an allosteric modulator of the $GABA_A$ receptor (Belelli & Lambert, 2005; Belelli et al., 2022), progesterone itself appears to change the subunit composition of the $GABA_A$ receptor (Gangisetty & Reddy, 2009; Gangisetty & Reddy, 2010; Reddy et al., 2012). Moreover, ALLO enhances inhibitory neurotransmission mediated by $GABA_A$ receptors, resulting in anaesthetic, analgesic, anxiolytic, and anticonvulsant effects (Legesse et al., 2023; Schumacher et al., 2007; Steckelbroeck et al., 2004). Similarly, isoallopregnanolone (3β,5α-tetrahydroprogesterone) can antagonize the effects of ALLO at $GABA_A$ receptors (Belelli & Lambert, 2005, Belelli et al., 2022).

Furthermore, progesterone increases brain-derived neurotrophic factor (BDNF) expression via a cPR-regulated mechanism, which might be related to the progesterone-related increase in AMPA receptor-mediated neurotransmission and increased excitability of CA1 neurons (Jodhka et al., 2009; Kapur & Joshi, 2021). Finally, progesterone, alone or in combination with estradiol, appears to increase neuromodulation via increased serotonin production (e.g., Bethea et al., 2000; Russo et al., 2003; Lima et al., 2010) as well as increased striatal dopamine signaling (e.g., Cabrera et al., 2002; Kritzer et al., 2003; Zhang et al., 2008).

5. Selective progesterone receptor modulators: focus on ulipristal acetate

Selective progesterone receptor modulators (SPRMs) are synthetic compounds designed to selectively modulate cPR activity, either by mimicking, blocking, or modifying the receptor's action (Rabe et al., 2018). SPRMs can act as (partial) agonists and/or antagonists depending on the tissue context and receptor isoform (DeManno et al., 2003; Islam et al., 2020). SPRMs impact cPR function by altering receptor conformation, influencing coactivator and corepressor recruitment, and selectively modulating gene transcription in a context-dependent manner (Islam et al., 2020; Bouchard et al., 2011).

The therapeutic potential of SPRMs has been demonstrated for gynecological conditions (Islam et al., 2020). Ulipristal acetate (UPA) is an SPRM used at high doses for emergency contraception (Brache et al., 2013) and at low doses for the treatment of uterine fibroids (Croxtall, 2012). It primarily acts as a progesterone receptor antagonist in various tissues (Whitaker et al., 2014), preventing circulating progesterone from binding to its receptor and thereby affecting progesterone metabolism and effects (Keenan, 2011; Rabe et al., 2018). Unlike other antiprogestins, such as mifepristone, UPA has minimal anti-glucocorticoid activity (Melis et al., 2012), making it suitable for long-term use. UPA can inhibit ovulation if the luteinizing hormone (LH) increase has not yet occurred (Gemzell-Danielsson & Meng, 2010), while maintaining estradiol at mid-follicular levels and inducing anovulation in most women (Chabbert-Buffet et al., 2018; Chabbert-Buffet et al., 2007; Whitaker et al., 2014), thus avoiding vasomotor side effects and long-term bone demineralization.

6. Preclinical evidence of the effects of progesterone on the brain

Animal studies have provided evidence of various molecular processes being modulated by progesterone, i.e., neurogenesis, synaptogenesis, myelination, and neurotransmitter signaling, with inconclusive results for neurogenesis *per se* (Griksiene et al., 2022; McEwen & Woolley, 1994; Pletzer et al., 2023). Progesterone has neuroprotective properties, contributing to the maintenance and repair of nervous tissue (e.g., Barha et al., 2011; Ciriza et al., 2006; Djebaili et al., 2005; Guennoun, 2020; Jones et al., 2005; Jodhka et al., 2009; Liu et al., 2009; Stein, 2011). It is unfortunate that most studies are performed in males and only few recent studies are performed in animals of both sexes. Hence, confirmation of these effects in female animals is still lacking.

While progesterone alone may increase neuronal proliferation in the dentate gyrus (Bali et al., 2012; Liu et al., 2010), combined administration of estradiol and progesterone does not alter neuronal proliferation (Bali et al., 2012; Chan et al., 2014; Kordower et al., 2010; Oboti et al., 2015). Thus, while estradiol appears to upregulate the formation of new neurons (Galea et al., 2006; Mahmoud et al., 2016; Wan et al., 2021), progesterone appears to be involved in the survival of existing neurons, as well as their integration into existing brain networks via synaptogenesis and myelination.

Various studies have consistently demonstrated increased synaptogenesis in various brain areas in response to progesterone (e.g., Baka et al., 2017; Barreto-Cordero et al., 2020; Bethea & Reddy, 2010; Chen et al., 2009; Li et al., 2019; Perrotti et al., 2000; Spencer et al., 2008), as well as increased myelination (Aryanpour et al., 2017; Gangisetty & Reddy, 2009; Ghoumari et al., 2020; Magnaghi et al., 2006; Schumacher et al., 2014; Swamydas et al., 2009).

7. Progesterone and its effects on the human brain and behavior

Supported by preclinical findings on how progestagens affect neurogenesis, synaptogenesis, and neuroprotection (Pletzer et al., 2023), increasing evidence points to human brain structure changes concomitant with fluctuations in progesterone, although the quantitative relationship between progesterone hormone levels and brain anatomy remains understudied and is accompanied by effects with inconclusive directions (Rehbein et al., 2021).

The effects of progesterone, potentially mediated by its neuroactive metabolite ALLO, have been observed also in terms of brain function, particularly in areas related to emotion and cognition and of relevance to mental health (Sundstrom-Poromaa et al., 2020). Endogenous fluctuations in progesterone throughout the menstrual cycle have indeed been associated with differential activation of corticolimbic regions during the performance of cognitive tasks or emotion processing in healthy individuals (Dubol et al., 2021). However, from a behavioral

point of view, cognitive function and, to a certain extent, emotion processing remain sparsely linked to such variations in progesterone levels and brain response, hindering conclusions (Sundstrom Poromaa & Gingnell, 2014). Furthermore, studying the effects of progesterone in the context of the menstrual cycle limits the generalizability of the results and leaves the underlying mechanisms undiscovered, as the effects may be confounded by other hormonal changes related to the menstrual cycle, as in the case of estradiol (Dubol et al., 2021). This limitation also applies to studies on combined oral contraceptives (Griksiene et al., 2022; Pletzer et al., 2023) and MHT (Comasco et al., 2014; Griksiene et al., 2022).

Pharmacological experiments in the context of neuroimaging assessments can be instrumental in advancing the mechanistic understanding of the effects of progesterone. In a double-blind, crossover, functional magnetic resonance imaging study, the neuronal and behavioral effects of progesterone were investigated twice during the early follicular phase of different menstrual cycles upon the administration of 400 mg progesterone or placebo in healthy females (van Wingen et al., 2007, 2008). The psychological assessment consisted of a brief emotional task, where participants had to indicate which emotional facial expression corresponded to the target emotion (van Wingen et al., 2008), followed by a memory task, where faces needed to be memorized and recognized (van Wingen et al., 2007). While progesterone had no effect on behavioral outcomes in the emotion task, it was associated with changes in neuronal activity, particularly in the amygdala and its connectivity with distant brain regions (van Wingen et al., 2008). Specifically, progesterone was associated with increased amygdala reactivity and functional connectivity with the dorsal anterior cingulate cortex (dACC) during emotion processing. In contrast to these findings, during the memory task, progesterone was associated with a reduction in amygdala activity and impaired memory performance, as shown by decreased recognition accuracy (van Wingen et al., 2007).

This paradoxical effect of progesterone on amygdala activity may be attributable to the differences between tasks but also to the study design, namely, the different progesterone levels during the implementation of each of the two tasks (van Wingen et al., 2007; van Wingen et al., 2011). While during the emotional task, serum levels of progesterone were in the range of the luteal phase, during the memory task (which took place later), progesterone reached concentrations commonly found in early pregnancy. This is supported by the detrimental effect on memory function observed during the follicular phase in females receiving 0.07 mg/kg ALLO (leading to third-trimester pregnancy serum concentrations), in comparison with placebo (Kask et al., 2008).

Therefore, a dose-dependent effect of progesterone on amygdala activity has been suggested, with a stimulating effect of progesterone at moderate levels and an inhibitory effect at higher doses. These effects may be mediated by ALLO, which has been shown to have an inverted U-shaped relationship with mood (Andréen et al., 2006; Bäckström et al., 2014, 2015). At both low and high doses, ALLO exerts anxiolytic effects, whereas moderate levels of ALLO may be associated with negative mood and manifest as premenstrual symptoms. This paradoxical anxiogenic effect of ALLO is analogous to the one exerted by other modulators of the $GABA_A$ receptor, such as benzodiazepines, which are usually anxiolytic but can also exhibit anxiogenic effects at certain doses (Bäckström et al., 2015). The opposing effects on amygdala activity could thus be explained by the nonlinear relationship with ALLO, increasing amygdala activation at moderate doses and inhibiting amygdala activation at high doses.

Taken together, progesterone-induced impairment in memory formation and retrieval, underlined by differential brain function, may for example help to explain cognitive complaints experienced by some females during pregnancy. The findings regarding the emotional task could contribute to the understanding of negative affect during the luteal phase of the menstrual cycle, especially in the context of PMDD. In fact, greater amygdala activation has been observed when emotional stimuli are processed during the luteal phase (Dubol et al., 2020; Stiernman et al., 2023). Therefore, heightened amygdala activation upon progesterone administration may suggest a neural mechanism by which progesterone, or ALLO, may increase anxiety and worsen mood in hormone-sensitive individuals. On the other hand, increased connectivity with top-down regulatory regions, such as the dACC and the fusiform gyrus involved in facial stimuli recognition, could indicate modulatory effects of progesterone on larger brain circuitries.

Despite offering unique insights into the behavioral effects and underlying mechanisms of progesterone, such pharmacological studies remain scarce. Furthermore, small sample sizes compromise the generalizability of the findings and warrant replication. Therefore, further investigations on the behavioral and neuronal effects of progesterone are needed, and caution is advised when interpreting existing findings.

8. Progestagens and stress

An acute stress reaction is an adaptive response to real or perceived threats, while chronic stress can have negative neurobiological, physiological, and psychological consequences, potentially leading to various physical and psychological disorders (Bell & Ross, 2014). A bidirectional relationship has been demonstrated between the HPG and the HPA (hypothalamic-pituitary-adrenal) axis, with the production of sex steroid hormones and stress hormones (glucocorticoids) being mutually influenced (Oyola & Handa, 2017; Phumsatitpong et al., 2021). Notably, in response to stress, the adrenal glands in both animals and humans release progesterone along with their respective primary glucocorticoid; corticosterone in many animal species and cortisol in humans (Herrera et al., 2016; Kalil et al., 2013). Likewise, the HPA axis activity seems to be influenced by menstrual cycle-dependent changes in hormone production via the HPG axis. A greater salivary cortisol response to an acute stressor has been observed during the luteal than the follicular phase (Kirschbaum et al., 1999; Montero-López et al., 2018), thus suggesting an effect of progesterone. In line, the autonomic nervous system (ANS) was found to exhibit a sympathetic predominance in the luteal phase of the menstrual cycle (Brar et al., 2015; Tada et al., 2017; Yazar et al., 2016). This reflects the body's adaptation to potential pregnancy and energy demands during this cycle phase, with increased activity in the sympathetic branch of the ANS influencing physiological parameters such as heart rate and blood pressure (Stadler et al., 2019).

Moreover, progesterone affects the stress response also through its neuroactive metabolite ALLO. In females, ALLO is synthesized from progesterone in the ovaries, adrenal glands, placenta and nervous system (Cáceres et al., 2024). This neurosteroid plays an important regulatory role in responding to acute stress, potentiating the effects of the GABAergic system, and its level decreases under chronic stress (Bali et al., 2016; Pisu et al., 2022). As the primary inhibitory neurotransmitter in the brain, GABA helps to maintain homeostasis and prevent overstimulation of the nervous system by dampening excessive neural activity during stress (Purdy et al., 1991; Schweizer-Schubert et al., 2021). Chronic stress is associated with blunted HPA axis activity and also altered ALLO levels, which may contribute to the development of stress-related disorders (Almeida et al., 2021). These characteristics suggest ALLO as a potential biomarker for stress-related disorders accompanied by hormone sensitivity not only to fluctuations in sex steroids but also concerning the response to regulatory stress mechanisms (Schiller et al., 2014; Schweizer-Schubert et al., 2021).

The discussed interactions between endogenous progesterone, ALLO, and stress support the assumption that synthetic progestins also influence the stress systems. Notably, most studies included users of combined HCs, it is thus unclear which of the observed effects are attributable to progestins or to estrogens, and/or their interactive effect (Gervasio et al., 2022; Laird et al., 2019; Lewis et al., 2019).

For instance, in studies comparing HC users and regularly cycling controls, differences in stress and inflammation markers such as altered HPA axis activity and reactivity of the ANS have been observed (Herrera et al., 2019; Masama et al., 2022; Mengelkoch et al., 2024; Nielsen et al.,

2013; Rohleder et al., 2003), though this may be due to the effect of ethinyl estradiol rather than progestins (Kangasniemi et al., 2022; Kangasniemi et al., 2023). Interestingly, progestins may affect stress and mood parameters depending on their level of androgenicity (Herrera et al., 2019), as some studies reported mood-stabilizing effects of HCs containing anti-androgenic progestins (Lopez et al., 2012) and adverse effects on stress and mood among users of HCs with androgenic progestins (Pletzer et al., 2023; Schaffir et al., 2016). However, cross-sectional comparisons are prone to selection bias, and may reflect individual sensitivity to progestins rather than pharmacological differences between different types of progestins.

Studies on progestagen-only contraception and the HPA-axis are very few. One cross-sectional study, by Aleknaviciute et al. (2017), provides initial evidence suggesting an association between levonorgestrel-IUD (LNG-IUD) and potentiated stress reactivity, both acutely under standardized laboratory conditions, as well as chronically under naturalistic conditions. Exaggerated salivary cortisol and a potentiated heart rate in response to the Trier Social Stress Test, as well as elevated levels of hair cortisol (as a proxy of long-term exposure to stress), was observed among LNG-IUD users compared with oral ethinylestradiol/levonorgestrel users and regularly cycling controls. Further, LNG-IUD and oral ethinylestradiol/levonorgestrel users had a blunted salivary cortisol response to adrenocorticotropic hormone administration, compared to controls (Aleknaviciute et al. 2017). On the other hand, a prospective cohort study found no differences in hair cortisol between LNG-IUD and copper IUD users (Doty et al., 2023).

The role of progestagens in the response to stress may have important implications for neuropsychiatric disease risk and resilience across the lifespan in females (Bale & Epperson, 2015). Stress-related disorders are more common in females than males (Bale & Epperson, 2017; Schweizer-Schubert et al., 2021; Solomon & Herman, 2009), thus urging the investigation of the biopsychological interactions between stress and progestagens. Additionally, there is also a lack of studies regarding the impact of such interactions on everyday life function that would allow to profile their ecological validity.

9. Progesterone receptor modulation: effects of ulipristal acetate on the brain and mood in patients with PMDD

PMDD presents itself as a model to study the impact of progesterone on the brain in relation to mental health (Dubol et al., 2020), as the cyclical occurrence of symptoms coincides with its fluctuations. While estradiol and progesterone levels do not differ from normative ranges in PMDD patients (Backstrom et al., 2014), fluctuations of the levels of these steroids have been proposed as triggers of PMDD symptomatology. Indeed, their suppression has been associated with symptom improvement (Nyberg et al., 2007; Schmidt et al., 2017; Schmidt et al., 1998; Segebladh et al., 2009; Wyatt et al., 2004).

The hypothesis that SPRMs may prevent progesterone from inducing negative effects has been tested with the aim of identifying a potential new treatment for PMDD. A randomized placebo-controlled trial demonstrated the efficacy of the SPRM UPA (5 mg per day) in reducing the psychological symptoms of PMDD, with negligible side effects (Comasco et al., 2021, see Fig. 3). The mean improvement in the daily record of severity of problems (DRSP) total score during the last premenstrual period was 41 % and 22 % in the treatment and placebo groups, respectively (mean difference, −18 %). The effects on mental health were most pronounced for depressive and anger/irritability symptoms. Complete or partial remission during the last premenstrual period was attained by 50 % and 35 %, respectively, in the treatment group. These findings expand on a borderline significant trend observed in a small sample tested with mifepristone (Chan et al., 1994) and the beneficial effects on self-reported premenstrual symptoms in women undergoing treatment with ulipristal acetate for uterine leiomyomas with PMS (Chen et al., 2017).

By modulating progesterones actions, the SPRM UPA has been

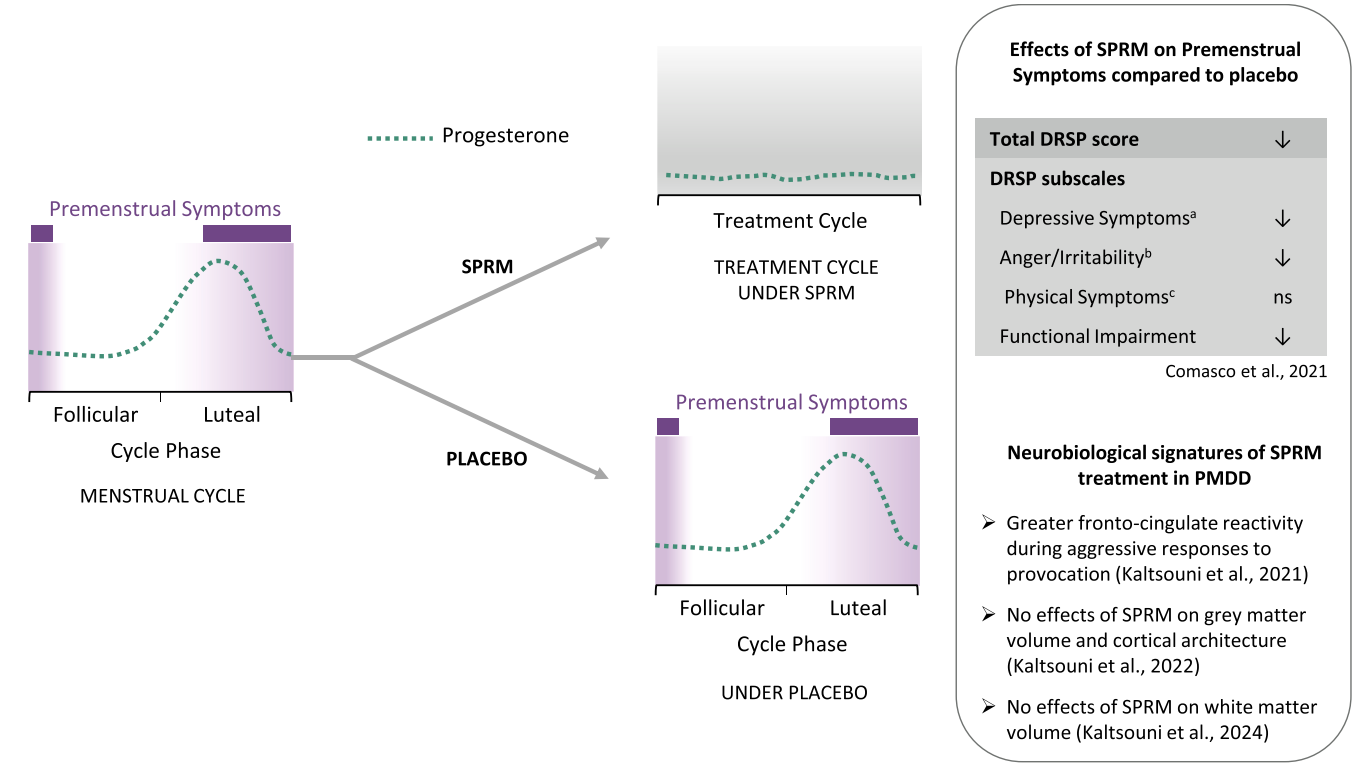

Fig. 3. Randomized controlled trial of pharmacological treatment of premenstrual dysphoria disorder with the selective progesterone receptor modulator 'ulipristal acetate' (for study details, see Comasco et al., 2021). SPRM = Selective progesterone receptor modulator. ns = non-significant effects. [a] This subscale includes symptoms of depressed mood; feelings of hopelessness, worthlessness and guilt; sleep difficulties; and feeling overwhelmed. [b] This subscale includes symptoms of anger, irritability, and interpersonal conflicts. [c] This subscale includes symptoms of breast tenderness, bloating, headache, and joint or muscle pain.

investigated to gain mechanistic insights into the role of progesterone in PMDD (Sundstrom-Poromaa et al., 2020). Recent pharmaco-neuroimaging research has begun to reveal the neural effects of SPRM treatment. Using multimodal neuroimaging techniques, scientists have mapped the structural and functional brain changes associated with symptom relief in PMDD patients before and during SPRM treatment. These findings indicate that SPRM treatment enhances reactivity in the dorsal anterior cingulate cortex and dorsomedial prefrontal cortex during aggressive responses to provocations (Kaltsouni et al., 2021, see Fig. 3). In contrast, more aggressive responses were linked to lower reactivity in these fronto-cingulate regions in the placebo group (Kaltsouni et al., 2021). Since aggressiveness is a potential outcome of core PMDD symptoms such as irritability and anger, these results suggest that progesterone receptor antagonism may improve top-down emotion regulation in PMDD. This is possibly achieved by enhancing the activation of brain regions involved in attentional control, cognitive control, and the regulation of negative emotions. In turn, this could explain the beneficial effects of SPRM treatment in reducing irritability, anger, and conflict, which involve responding to salient stimuli, evaluating potential behavioral responses, and controlling immediate input. Conversely, the anatomical properties of the brain seem to remain unchanged upon SPRM treatment (Kaltsouni et al., 2022; Kaltsouni et al., 2024, see Fig. 3), suggesting that structural variations do not explain PMDD symptom relief. This finding is further supported by brain structure alterations found in patients with PMDD compared to controls across both symptomatic and asymptomatic menstrual cycle phases, indicating trait vulnerability markers of PMDD (Dubol et al., 2024). Thus, in addition to proposing SPRM as a potential new treatment for PMDD (Comasco et al., 2021, see Fig. 3), these results provide new insights contributing to advancing our understanding of the influence of progesterone on female's brain and mental health (Fig. 3).

10. Progesterone's metabolite allopregnanolone and perinatal depression

As a friend vs. foe, progesterone exerts beneficial effects on another female-specific psychiatric disorder such as PND, compared with the detrimental effects observed in the case of PMDD (Sundstrom-Poromaa et al., 2020). Such negative effects in PMDD are likely explained by the impact of ALLO on mood, as proven by successful trials inhibiting it or its synthesis, or targeting its allosteric modulation (Sundstrom-Poromaa & Comasco, 2023). On the other hand, the continuous intravenous administration of ALLO/brexanolone is used to treat PND (Meltzer-Brody et al., 2019), and the beneficial effects of its more viable counterpart zuranolone have launched it as a rapid-acting, oral, and well-tolerated treatment (Deligiannidis et al., 2023). PND is suggested to be triggered by sensitivity to hormonal withdrawal experienced upon giving birth (Skalkidou et al., 2012). This is the first time that a hormonal treatment has been successfully approved for a female-specific psychiatric disorder, sparking interest, as demonstrated by research on zuranolone as a potential treatment for major depressive disorder (Gunduz-Bruce et al., 2019), although it has been tested for only 14 days (Ten Doesschate et al., 2022). Explorative research on the therapeutic use of ALLO in the treatment of mood disorders and other neurological conditions is therefore warranted.

11. Synthetic progestins and the brain

Bürger et al. (2021) conducted the first review on the impact of LNG-IUDs on stress, mental health, and brain architecture. Besides the lack of studies on the brain, variation in study design, population, and quality of methods was the major observation regarding the literature, thus calling for systematic research on the effects of progestin-only HCs such as LNG-IUDs on the brain and mental health.

Recently, a national cohort study using Danish register data on first-time users of LNG-IUDs provided strong evidence of a dose-dependent association between parenteral LNG administration and incident depression (Larsen et al., 2024), backing findings of previous national health registry-based studies (Skovlund et al., 2018; Stenhammar et al., 2023). In addition, two recent papers on cross-sectional EEG investigations demonstrated greater amplitude of the attention-related component (N2, EEG) during emotion regulation task in LNG-IUD users compared to COC users or regularly cycling controls (Zelionkaitė et al., 2024), but found no differences in resting stated EEG parameters (alpha power, individual alpha peak frequency, and aperiodic activity) between these groups (Gaižauskaitė et al., 2024). As suggested by reviews and case reports, methodologically well-designed studies on LNG-IUDs and the brain are lacking and more research is warranted (Bürger et al., 2021; Elsayed et al., 2023; Zeiss et al., 2020).

Otherwise, the impact of combined HC and MHT on the brain and different aspects of cognition (e.g., visuospatial, social) seems to vary depending on the progestin contained though such effect cannot be fully disentangled from estrogenic effects (Beltz, 2022; Song et al., 2023). Randomized controlled trials shall be performed to rule out individual differences in sensitivity to progestins when comparing COCs containing different progestin types (e.g. androgenic vs. anti-androgenic progestins).

12. Progestagens and perimenopause

The menopausal transition is associated with symptoms such as hot flashes and sleep problems, and, for some individuals, an increased susceptibility to mood disorders, such as depression (Badawy et al., 2024), and increased vulnerability to stress and cognitive decline (Monteleone et al., 2018; Weber et al., 2014). However, the underlying mechanisms are still poorly understood, and little attention has been given to investigating the role of progestagens in (peri)menopausal symptoms and the effects of MHT. Postmortem analyses of the brain tissues of postmenopausal women revealed the accumulation of progesterone in the amygdala, cerebellum, and hypothalamus (Bixo et al., 1997), suggesting local synthesis of progestagens in the brain even postmenopausally (Labrie, 2015).

MHT appears to have modulatory effects on brain regions associated with cognitive function, as well as on the cholinergic and serotonergic systems, while the emotional brain remains understudied. There is evidence that progestagens counteract the neural effects of estrogens during MHT. However, as estradiol supplementation is the prerequisite for relief of the menopausal symptoms, no studies on progestin-only treatment in perimenopausal women are available (Comasco et al., 2014; Griksiene et al., 2022).

MHT commonly improves mood, but the progestagen component in combined MHT might counteract the beneficial effect of estrogen or induce negative mood in asymptomatic females (Toffol et al., 2015). For synthetic progestins, small randomized trials comparing medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA) have shown reduced depressed mood with MPA combinations in both sequential and continuous combined treatments (Bjorn et al., 2000; Odmark et al., 2004), but the overall evidence is weak. Two randomized controlled trials on oral bioidentical progesterone did not find progesterone to counteract the beneficial effect of estrogen on mood (Gleason et al., 2015; Gordon et al., 2018), whereas two separate randomized clinical trials on estradiol together with oral and vaginal progesterone, respectively, found that bioidentical progesterone does induce negative mood (Andréen et al., 2005; Andréen et al., 2006). However, the effects of progesterone on mood seem to depend on the level of metabolism to ALLO and individual vulnerability to hormonal fluctuations (Backstrom et al., 2015).

Cognitive complaints are common during peri- and postmenopause (Edwards et al., 2019; Reuben et al., 2021) but to date, there is consensus that MHT is not useful for improving cognition in postmenopausal women with cognitive decline (Hogervorst et al., 2009). Instead, combinations with MPA seem to increase the risk of dementia,

as shown in the large Women's Health Initiative Memory Study (Shumaker et al., 2003). In previously healthy women, MPA also stands out as a possible risk factor for cognitive impairment compared with combinations with NETA, levonorgestrel, dienogest (Griksiene et al., 2022) or micronoized progesterone (Memi et al., 2024). Worth to note, in a randomized controlled trial, bioidentical progesterone in combination with different estrogens did not affect cognition in early menopause (Gleason et al., 2015). On the other hand, ALLO, MPA, and some MPA metabolites with GABAergic effects have been shown to cause memory impairment in animal studies (Bengtsson et al., 2016; Das et al., 2022), indicating that not all effects observed in the animal brain could be easily translated to humans. It is also difficult to compare different progestagens in terms of their effects on mood and cognition, as both are influenced by the nature of the progestagen used, the regimen, dose of progestagen and/or estrogen, administration route, timing, and individual risk factors.

13. Progestagens and neuroprotection

Progestagens, including progesterone, its metabolites, and its synthetic derivatives, have demonstrated protective effects in animal models of neurodegenerative diseases such as Alzheimer's disease (AD) as well as traumatic brain injury, and stroke (Guennoun et al., 2019; Guennoun et al., 2020; Melcangi et al., 2012; Melcangi et al., 2014; Schumacher et al., 2014; Irwin and Brinton 2014). However, translation to clinical medicine has not always been straightforward.

Regarding neuroprotection by progestagens in AD, in a preclinical model using 3xTg-AD mice, progesterone treatment was associated with lower hyperphosphorylation of the protein Tau stabilizing brain cell structure (Carrol et al., 2007) and ALLO treatment promoted neuroregeneration and cognitive function; decreased neuroinflammation and the accumulation of beta-amyloid; and restored the deficits of bioenergetics (Irwin & Brinton, 2014). Results of a phase 1b/2a clinical trial on ALLO as a regenerative therapeutic for AD indicated that the rate of decline in hippocampal volume was slowed, and in some cases reversed, in the ALLO group compared to placebo (Raikes et al., 2022). Gain of hippocampal volume was evident in *APOE* ε4 carriers. ALLO as a regenerative therapeutic for mild Alzheimer's disease has entered phase 2: A multi-center, double-blind, randomized, placebo-controlled proof-of-concept efficacy clinical trial is currently in progress (REGEN-BRAIN study; NCT04838301).

Remarkable neuroprotective effects of progesterone in traumatic brain injury (TBI) were demonstrated in a large number of preclinical studies using animal models of TBI and two phase 2 clinical trials (Wright et al., 2007, Xiao et al., 2008). However, two large, multicenter, randomized and placebo-controlled Phase 3 trials (ProTECT III and SyNAPSE) did not find clinical benefits of progesterone for TBI (Wright et al., 2014; Skolnick et al., 2014) and a meta-analysis including five randomized clinical trials failed to show efficacy of progesterone to decrease mortality or disability after TBI (Ma et al., 2016). Multiple reasons for the failure of the clinical trials have been extensively discussed (Stein 2015; Schumacher et al. 2016; Ma et al., 2016; Guennoun, 2020).

Regarding neuroprotection by progestagens, stroke has also been investigated. Stroke is the leading cause of acquired disability and the second leading cause of dementia (Feigin et al., 2009; Lo et al., 2003) and mortality (Feigin et al., 2021). The incidence and outcomes of ischemic stroke are significantly influenced by both age and sex, with age being the greatest non-modifiable risk factor. While lifetime stroke rates are typically higher in males (Popa-Wagner et al., 2020; Rothwell et al., 2004; Roy-O'Reilly & McCullough, 2018), after menopause, the risk of stroke in females exceeds that of age-matched males, along with higher morbidity and mortality, and more difficult recoveries (Appelros et al., 2009; Fukuda et al., 2009; Glader et al., 2003; Mozaffarian et al., 2016; Niewada et al., 2005; Petrea et al., 2009; Roger et al., 2011; Roquer et al., 2003). This difference is thought to be related to hormonal changes. During their fertile years, women seem protected against stroke by ovarian hormones such as estrogen and progesterone, in line with animal models (Alkayed et al., 1998; Selvamani et al., 2014). A major factor contributing to this observation may be the variation of the levels in neuroprotective steroids within the brain. Following stroke, endogenous neuroprotective processes are triggered to counteract ischemic damage, with neuroactive steroids like progesterone and its metabolites potentially playing a role (Guennoun et al., 2019; Zhu et al., 2017).

Several studies have described the neuroprotective benefits of progesterone treatment in stroke models, highlighting its versatile use as a neuroprotective agent (Wali et al., 2016; Gaignard et al., 2016; Gibson et al., 2011). Progesterone has been shown to mediate cerebroprotection by regulating critical processes such as edema formation, neurotoxicity, blood–brain barrier integrity, inflammation, and mitochondrial functions (Guennoun et al., 2019). In both young male and female mice, progesterone preserved mitochondrial function and reduced oxidative damage after middle cerebral occlusion (MCAO) (Gaignard et al., 2016). Post-ischemic administration of progesterone to ovariectomized mice improved neurological outcome with no effect on lesion volume, while in aged female mice it significantly reduced lesion volume but did not improve neurological outcomes (Gibson et al, 2011). Transgenic male mice lacking neural PR expression showed larger ischemic brain infarcts and increased motor dysfunction, demonstrating the importance of PR-dependent mechanisms in protecting the brain post-stroke and highlighting the importance of neural PRs in mediating protective effects of endogenous progesterone (Zhu et al, 2017). PR is a key player for the mediation of the beneficial effects of progesterone (Liu et al., 2012; Zhu et al, 2019), suggesting that targeting PR could be a viable strategy for enhanced recovery after stroke. However, most studies have been performed in young, male mice. In contrast to progesterone, treatment with ALLO reduced brain edema, infarct volume, and improved functional outcomes by a signaling mechanisms independent of PR, as evidenced by its efficacy in PR knockout mice (Liu et al., 2012). As a positive modulator of $GABA_A$ receptors, ALLO may counteract the excitotoxicity in response to stroke.

Progestins have been designed to target the PR, and given the established importance of PR in neuroprotection, these compounds emerge as promising candidates for stroke treatment. Segesterone acetate (16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3, 20-dione) is a 19-norprogesterone derivative and selective agonist for PR without interacting with other steroid receptors (Sitruk-Ware et al., 2024). It was initially investigated for hormonal contraception and hormonal therapy; recent studies have shown its beneficial effects in the central nervous system and suggest that it could be a promising complementary treatment for stroke (Fréchou et al., 2021; Sitruk-Ware et al., 2024). Desogestrel and drospirenone are progestins commonly used in hormonal contraceptives and have been found to improve neurological scores and reduce infarct volumes in experimental stroke-induced brain injury (El Amki et al., 2019).

Remarkably, potential cerebroprotective effects have been associated with HC use. While COC use increases the risk of myocardial infarction or ischemic stroke depending on estrogen dosage (Gillum et al., 2000; Roach et al., 2015), oral progestin-only HC use does not increase the risk of developing various cardiometabolic outcomes (Glisic et al., 2018). Advancements in our knowledge of how progesterone and its synthetic variants function in cerebroprotection can lead to the development of females specific therapies to improve outcomes, not only in stroke patients but also in HC users.

14. Methodological considerations and future perspectives

The scarcity of studies carried out in female subjects is a major hindrance to our understanding of the effect of progesterone, ALLO, and progestins across the female reproductive life. Remarkably, major methodological issues need to be overcome, including small sample sizes, a lack of longitudinal data, a loose assessment of hormonal

profiles, and poor characterization of study participants. Experimental evidence disentangling the effects of progesterone on the human brain, mood, stress and cognition is extremely scarce, as exemplified by the single study-findings described in this review. Moreover, studies on puberty, the menstrual cycle, pregnancy, perimenopause, HC, and MHT are hampered by the difficulty to assess the individual effects of progestagens vs. the effects of estrogens. Another shortcoming in the current research landscape is the lack of studies investigating to what extent progestagen affect the daily life of females who are naturally cycling, pregnant, menopausal, on MHT, or using HC.

Placebo-controlled trials are advancing our knowledge of the efficacy and safety profile of progestagens and SPRM treatments, including side effects and contraindications. Nevertheless, their rare combination with neuroimaging and behavioral assessments limits a mechanistic understanding of the role of progesterone in brain health. On the other hand, crossover trials in which each participant acts as own control are needed to rule out individual differences in neuropsychological response to the various types of progestins included in HC. Important to note are also progestagen metabolites and their biological activity (Stanczyk et al., 2024), as for example those structurally related to progesterone (e.g., MPA), for which little is known but are widely used in HC or MHT.

Overall, studies of the interaction between progestins, stress, and mood show mixed results, with the underlying mechanisms and their implications for everyday life remaining unclear (Jentsch et al., 2022). Potential explanatory factors are not only the investigation of COC that include estrogens, but also the cross-sectional design, comparison group, lack of considerations of progestin type, dosage, route of administration, timing, and absence of ecologically valid study designs. Further, more research is warranted on interactions of different progestins with other steroid hormone receptors (androgen, estrogen, mineralocorticoid, and glucocorticoid receptors) and progesterone receptor affinity itself, which is up to four times greater for some progestins than for endogenous progesterone (Africander et al., 2014; Griksiene et al., 2022; Hapgood et al., 2014; Pletzer et al., 2023). This knowledge gap should be targeted comprehensively in future research, as initial findings point to substantial differences in the effects of different progestins on the brain. For example, MPA seems to exert undesirable effects on brain tissue and cognition, whereas endogenous progesterone and other progestins even have neuroprotective effects and slow cognitive decline (Griksiene et al., 2022). To target some of those questions in a more structured manner, animal models may be required (Tronson & Schuh, 2022).

Progesterone and compounds that target PR as well as ALLO are beneficial after stroke, as they can preserve tissue and improve functional outcomes, presenting a new potential treatment strategy (González et al., 2020; Guennoun et al., 2019; Guennoun, 2020; Sitruk-Ware et al., 2024; Melcangi et al., 2014). Advancements in our knowledge of how progestagens and their synthetic variants function in cerebroprotection in young and aged females can lead to the development of sex- and age- specific therapies to improve outcomes in patients with stroke but also contribute to minimize adverse cardiovascular effects on the brain of HC users.

15. Conclusions

The present review highlights the effects of progestagens on the brain, mood, stress, cognition, and cerebroprotection in females, as an area where further research is needed. To date, experimental pharmacological research on progesterone/progestins-only effects is confined to single studies including small samples. The rest of the literature is limited by the nested effects of progestagens and estrogens. The therapeutic efficacy of SPRMs for PMDD and of ALLO for PND paves the way for new sex-specific treatments and a deeper understanding of the neuroendocrine mechanisms involved in the mental conditions in females.

Authors contributions

All authors contributed to drafting the paper and critically revised it.

CRediT authorship contribution statement

Celine Bencker, Laura Gschwandtner: Writing – review & editing, Writing – original draft. **Sibel Nayman:** Writing – review & editing, Visualization. **Inger Sundström-Poromaa, Billie Nguyen, Urs M. Nater:** Writing – review & editing. **Rachida Guennoun, Ramunė Grikšienė:** Writing – review & editing, Writing – original draft. **Belinda Pletzer:** Writing – original draft. **Marie Bixo:** Writing – review & editing, Writing – original draft. **Erika Comasco:** Writing – review & editing, Writing – original draft, Conceptualization.

Funding

Science for Life Laboratory; Swedish Research Council; Swedish Society of Medicine;

Celine Bencker is a recipient of a DOC Fellowship of the Austrian Academy of Sciences at the Institute of Clinical and Health Psychology of the University of Vienna (26796).

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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