Progesterone, progestagens and the central nervous system

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Oestrogen, progestagens and androgens are able to modulate several brain functions. Receptors for gonadal steroids have been identified in several brain areas: amygdala, hippocampus, cortex, basal forebrain, cerebellum, locus coeruleus, midbrain rafe nuclei, glial cells, pituitary gland, hypothalamus and central grey matter. The mechanism of action of sex steroids at this level is similar to that observed in the peripheral target organs, including both genomic and non-genomic effects. The increased use of sex steroid hormone derivative therapies has lead to study of the biochemical and metabolic properties of the different progestin molecules available in hormonal therapies. In particular, experimental and clinical studies focused the attention of researchers on interactions between oestrogens and progestins in the neuroendocrine control of the brain functions and its clinical implications. Moreover, steroids are also synthesized \textit{de novo} in the brain or may be derived from the conversion of blood-borne precursors, suggesting that the brain is also a source of steroids, named neurosteroids. Neurosteroids exert non-classical rapid actions as allosteric agonists of \(\gamma\)-aminobutyric acid receptor A (GABA\textsubscript{A}) and also modulate classic neurotransmitters in the brain. In addition, progesterone derivatives, e.g. pregnanolone, and 3\(\alpha\) 5\(\alpha\)\textsubscript{-}OH THP (allopregnanolone) are synthesized \textit{de novo} by astrocytes and oligodendrocites starting from cholesterol. Physiological or pathological modifications of the synthesis and release of neurosteroids play a relevant role in the control of brain function.

\textit{Key words:} androgens/CNS/oestrogen/progestagens

Introduction

The brain is an organ whose development and activities are modulated by several endogenous and exogenous stimuli and there is a large body of evidence that
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Noradrenaline
Dopamine
Serotonin
Acetyl choline
β - endorphin
NPY
CRF
GABA
Melatonin
GnRH
SRH
TRH
CGRP

oestrogens
progestins
androgens

Figure 1. Neurotransmitters and neuropeptides modulated by sex hormones. NYP = neuropeptide Y; CRF = corticotrophin-releasing factor; GABA = γ-aminobutyric acid; GnRH = gonadotrophin-releasing hormone; SRIH = serotonin receptor inhibiting hormone; TRH = thyrotrophin-releasing hormone; and CGRP = calcitonin gene-related peptide.

indicates the actions of sex steroid hormones within the brain. Endogenous and exogenous steroid hormones are able to modulate brain function through the binding with specific receptors. Receptors for gonadal steroids have been identified in several brain areas: amygdala, hypopocampus, cortex, basal forebrain, cerebellum, locus coeruleus, midbrain rafe nuclei, glial cells, pituitary gland, hypothalamus and central grey matter (Speroff et al., 1995; Alonso-Soleis et al., 1996; Genazzani et al., 1996).

The mechanism of action of oestrogens, androgens and progestins in the brain is similar to that observed in the peripheral target organs, including both genomic and non-genomic effects. Through the classical genomic mechanisms, steroids induce slower long-term actions on neurons by activating specific intracellular receptors that modulate gene transcription and protein synthesis. Thus, gonadal steroids modulate the synthesis, release and metabolism of many neuropeptides and neuroactive transmitters and the expression of their receptors (Figure 1) (Alonso-Soleis et al., 1996; Panay and Studd, 1998; Sundstrom et al., 1999). In particular, among the neurotransmitters, noradrenaline, dopamine, γ-aminobutyric acid (GABA), acetylcholine, serotonin and melatonin are regulated by sex steroid hormones. The neuropeptides directly modulated by gonadal hormones include opioid peptides, gonadotrophin-releasing hormone (GnRH), corticotrophin-releasing factor (CRF), neuropeptide Y (NPY) and galanin.

On the other hand, steroid hormones exert very rapid effects that cannot be attributed to genomic mechanisms. In fact, throughout specific non-genomic mechanisms, oestrogens, androgens and progestagens modulate electrical excitability, synaptic functioning, and morphological features (Fuxe et al., 1981; Matsumoto, 1991; McEwen and Wooley, 1994; Mong and McCarthy, 1999). The interaction of genomic and non-genomic mechanisms allows for a wide range of sex steroid actions in the regulation of cerebral functions.

Classical knowledge and recent developmental data on the effects of sex
Steroid hormones on the brain are derived by in-vitro and in-vivo studies. Only a few clinical trials have been carried out on the effects of exogenous sex steroids on the central nervous system (CNS) in humans. The increased use of sex steroid hormone derivative therapies has lead to studies of the biochemical and metabolic properties of the different progestin molecules available in hormonal therapies. In particular, attention has been focused on the interactions between oestrogens and progestins in the neuroendocrine control of the brain functions and its clinical implications. In fact, each progestin molecule is able to bind to the progesterone receptor and exert its specific progestative effect. However, the different kinds of molecules may either interfere with other sex steroid hormone or other substance receptors, thus exerting multiple effects in each target tissue.

The identification in the CNS of steroids synthesized de novo or derived from blood-borne precursors has suggested that the brain is not only a target but also a source of steroids, named neurosteroids (Mellon, 1994). Progesterone is not only produced in the ovaries and adrenal gland but it is also synthesized in the cerebral glial cells and for this reason is considered a neurosteroid. Progesterone derivatives such as pregnanolone, and 3α 5α-OH THP (allopregnanolone) are also synthesized de novo by astrocytes and oligodendrocites starting from cholesterol. Neurosteroids exert non-classical rapid actions as allosteric agonists of GABA receptor A (GABA_A) and also modulate classic neurotransmitters in the brain (Mellon, 1994). Several studies have shown a relationship between the fluctuation of the synthesis and release of neurosteroids and psychological symptoms, e.g. depression, anxiety and irritability (Paul and Purdy, 1992; Mellon, 1994).

**Progestins and CNS: experimental studies**

Progesterone and its derivative compounds modulate the synthesis and the release of several neurotransmitters and neuropeptides in response to specific physiological or pathological stimuli. In particular among the brain areas, the hypothalamus and the anterior pituitary lobe are considered the two principal targets of androgens, oestrogens and progestagens. At the hypothalamic level, the principal target for sex steroid hormones are those neurons producing the pulsatile release of GnRH. The release of GnRH depends upon the complex and co-ordinated inter-relationships between gonadal steroids, pituitary gonadotrophins and neuroendocrine systems. The interplay of these control mechanisms is governed by peripheral feed-back signals, but the input from higher brain areas may also modify the GnRH secretion. The anterior pituitary lobe is the best-known target tissue for endogenous or exogenous sex steroid hormones. It is possible to detect luteinizing hormone (LH) and follicle stimulating hormone (FSH) as the expression of pituitary cell activity. The synthesis and release of FSH and LH by gonadotrophic cells depends upon the peripheral control of gonadal hormones and the hypothalamic GnRH.

In the literature, several pieces of data are available on the effects of oestrogens
and progestagens on the hypothalamus and anterior pituitary in experimental models. Experimental studies on female rats show a significant increase in the hypothalamic concentration of GnRH after surgical ovariectomy when compared with fertile control rats (Mishell et al., 1977; Genazzani and Petraglia, 1990). Oestradiol benzoate treatment induces a significant reduction in GnRH concentration to values similar to those found in fertile rats. Moreover, the treatment of ovariectomized female rats with oestradiol benzoate in association with different types of progestins, progesterone, norethisterone enantate (NET), desogestrel and medroxyprogesterone acetate (MAP), induced different results with respect to rats given oestradiol alone (Mishell et al., 1977; Genazzani and Petraglia, 1990). Progesterone and NET treatment increased GnRH concentrations in the mediobasal hypothalamus of ovariectomized rats, while the rats treated with desogestrel or MAP did not show any changes in GnRH concentrations compared with ovariectomized rats. When progestins were chronically administered with oestradiol benzoate, progesterone and NET reversed the effects on the GnRH induced by oestradiol benzoate alone, while desogestrel and MAP were not active in rats (Mishell et al., 1977; Genazzani and Petraglia, 1990).

At the pituitary level, the content of LH was significantly higher in ovariectomized rats than in fertile control rats. The administration of oestradiol benzoate alone to ovariectomized rats induced a significant increase in LH that counteracted the effect of ovariectomy. The chronic treatment of ovariectomized rats with progesterone or NET alone significantly reduced LH concentration. Desogestrel and MAP administration did not induce significant changes. All progestins, given in association with oestradiol benzoate in ovariectomized rats, blocked the increase in LH induced by oestradiol benzoate alone (Mann and Barraclough, 1973; Genazzi et al., 1990). Surgical ovariectomy induced a significant increase in plasma LH concentrations in fertile female rats, while oestradiol benzoate administration reduced circulating LH concentrations to values similar to those of the fertile control group. Progesterone and different progestins were inactive in counteracting the effects of oestradiol benzoate on plasma LH concentrations in rats (Mann and Barraclough, 1973; Mishell et al., 1977; Labrie et al., 1979; Genazzani and Petraglia, 1990; Bohus et al., 1991).

In summary, these data support the evidence that progesterone and NET may act on the hypothalamus–pituitary axis. Desogestrel and MAP did not influence the inhibitory effects of oestradiol benzoate at the hypothalamic level, but all gestagens were able to modulate the oestrogen effects on pituitary cells.

Gonadal hormones modulate the activity of the hypothalamic and extra-hypothalamic noradrenergic, dopaminergic, serotonergic neurons (Figure 2). Experimental trials in castrated female rats showed an impairment of the catecholaminergic neurons with an increase in noradrenaline release and a decrease in dopamine. Oestrogen administration was able to decrease the release of noradrenaline, to increase the dopaminergic neuronal activity and the dopamine release from the medio–basal hypothalamus. The effect of oestrogens in modulating adrenergic receptors appears to be bimodal by up-regulating the α1-edrenergic and down-regulating the β-adrenergic receptor activity (Plotsky
et al., 1989; Bohus et al., 1991; Etgen and Karkanias, 1994). Few data are available regarding the effects of progesterone and progestins in experimental or clinical models on the catecholaminergic system. The association of progesterone and oestrogen in ovariectomized female rats suppressed oestrogenic effects on noradrenergic neurons in the pineal gland (Etgen and Karkanias, 1994). In the rabbit, oestradiol and progesterone enhance noradrenaline release, leading to an increase of the hypothalamus neuronal activity and to the expression of lordosis behaviour (Etgen and Karkanias, 1994; Genazzani et al., 1996; Panay and Studd, 1998).

The serotoninergic system is also modulated by gonadal steroids. In female rats, the hypothalamic serotonin content varies throughout the oestrus cycle and it has been demonstrated that oestradiol produces an acute biphasic up- and down-regulation of serotonin receptors: an early increase in serotonin receptors concentration is followed by a delayed decrease (Biegon et al., 1980). Oestrogens can also modify the concentration and the availability of serotonin, by increasing the rate of degradation of monoamino oxidase (MAO), the enzyme that catabolizes serotonin (Luine and McEwan, 1977). Experimental data have demonstrated that oestrogen displaces tryptophan from its binding sites to plasma albumin (in this manner tryptophan is more available in the brain to be metabolized into serotonin) and enhances the transport of serotonin (Luine and McEwan, 1977). In animal studies, progesterone increased serotonin turnover in ovariectomized rat in the limbic structures (Dickinson and Curzon, 1986). The effects of progesterone following stress altered the 5-hydroxytryptamine (5-HT) metabolism in several regions of the rat brain: 5-HT concentration are significantly higher when compared to those of rats stressed alone (Ladisch, 1977). Moreover, the activity of MAO and catechol-O-methyl transferase (COMT) in rat brain is increased by progesterone treatment (Luine et al., 1975; Holzbauer and Youdin, 1993).

Neuropeptides, e.g. NPY and galanin, influence central behaviour and neuro-
endocrine functions by stimulating the pulsatile release of GnRH and gonadotrophins. Experimental studies showed that oestrogens are able to stimulate the NPY synthesis and release in the hypothalamus. In castrated female rats, gonadal steroid deficiency reduces neurosecretion of NPY-producing neurons (Speroff et al., 1995; Panay and Studd, 1998). Oestrogen administration increases NPY content in the median eminence and the synthesis of NPY in arcuate nucleus, by inducing NPY gene expression. Indeed, recent findings demonstrate several interactions between NPY and β-endorphin neurons in the hypothalamus, and hence both oestrogens and progestagens may indirectly exert modulatory effects on NPY, inducing β-endorphin release. Galanin is a 29 amino acid neuropeptide isolated from the anterior pituitary gland of rats and humans, whose synthesis is under the control of oestrogen (Kaplan et al., 1988).

Galanin stimulates the hypothalamic GnRH release through a prostaglandin E2 (PGE2) and α1-adrenoreceptor-related mechanism and a common pulse-generator modulation between galanin and NPY has been postulated (Kaplan et al., 1988).

Among those neuropeptides regulated by gonadal steroids, endogenous opioids exert inhibitory or stimulatory signals on GnRH hypothalamic neurons. Oestrogens directly modulate endogenous opioid activity and directly stimulate opioid receptor expression. In particular, attention has been focused on β-endorphin, the most important and biologically active endogenous opioid peptide, that shows behavioural, analgesic, thermoregulatory and neuroendocrine properties (Genazzani and Petraglia, 1984; Etgen and Karkanias, 1994). Experimental and clinical studies have demonstrated that variations in central and peripheral β-endorphin concentrations may be considered as one of the markers of neuroendocrine functions (Adler et al., 1980; Aleem and McIntosh, 1985; Genazzani and Petraglia, 1988). Experimental evidence shows that β-endorphin reduces circulating LH concentrations by inhibiting GnRH secretion and decreasing sexual activity (Genazzani and Petraglia, 1987). Changes in hypothalamic and pituitary β-endorphin content and serum concentrations has been related to the oestrous cycle in rats, thus suggesting a role for oestrogens and progesterone in the control of the peptide synthesis and release. In-vitro experimental evidence suggests that the injection of β-endorphin is able to decrease circulating LH concentrations by inhibiting the release of GnRH. Chronic treatment with progesterone or different progestins (MAP, NET, desogestrel) with or without oestradiol benzoate administration induces different effects on the hypothalamic and pituitary content of β-endorphin in ovariectomized female rats (Genazzani and Petraglia, 1990). In the anterior pituitary lobe, the effect of the ovariectomy was a significant reduction in β-endorphin concentrations in comparison with fertile rats, while the administration of oestradiol produced a restoration of the β-endorphin content. When progesterone, NET or MAP were given alone, they did not modify the concentrations of the peptide while the concentrations significantly increased after desogestrel administration. In ovariectomized rats, the treatment with oestradiol benzoate plus progestins reversed the effect induced by oestradiol benzoate alone (Genazzani and Petraglia, 1990). In the
neurointermediate lobe. Ovariectomy in female fertile rats produced a decrease in β-endorphin content. The treatment with oestradiol benzoate alone or with progesterone, desogestrel and MAP induced an increase in β-endorphin concentrations to the values of fertile controls, while NET was not active in counteracting the effect of the ovariectomy. Progesterone and progestin treatment, in association with oestradiol benzoate, did not modify the effect of oestradiol benzoate alone (Genazzani and Petraglia, 1990). At the hypothalamic level, surgical ovariectomy did not modify β-endorphin concentrations in the hypothalamus of female rats. The administration of oestradiol benzoate, NET and progesterone in ovariectomized rats induced a significant increase in peptide concentrations, while desogestrel and MAP were inactive (Backstrom et al., 1983).

**Progestagens and CNS: clinical findings**

Generally, an association has been reported between oestrogen and the amelioration of mood and well-being in women, while the effects of progesterone and progestagens are considered to be negative. In fact, a close relationship between mood and behavioural impairment and hormonal variations may occur during the menstrual cycle. In particular, symptoms are related to the cyclic modifications of synthesis, release and circulating concentrations of oestrogens, progestagens and androgens. Generally, the follicular and pre-ovulatory phase are periods related to a state of well-being. These two phases are characterized by higher circulating concentrations of oestradiol (Backstrom et al., 1983). After ovulation starts, a progressive increase of negative mood symptoms occurs in relationship to the rise in circulating progesterone concentrations. The symptom peak occurs 5–6 days after the maximum progesterone concentrations at the mid-luteal phase. The symptoms were most severe during the last 5 premenstrual days, thus inducing so-called premenstrual syndrome in many women. In non-ovulatory cycles (either spontaneous or induced by GnRH agonist treatment), the symptom variations disappear (Muse et al., 1984; Hammarback and Backstrom, 1988; Hammarback and Ekholm, 1991; Mortola et al., 1991; Mezrow et al., 1994).

It is possible to divide the exogenous administration of sex steroid hormones into oestro–progestin administration in fertile women and hormone replacement therapy (HRT) in post-menopausal women. The increased use of sex steroid hormone derivatives in the last 30 years has led to the study of the biochemical and metabolic properties of the different molecules available in hormonal therapies. In particular, attention has been focused on the interactions between oestrogens and progestins in the control of psychophysical functions, mood, well-being and cognitive functions.

The oestrogen used in contraceptive pills is ethinyl oestradiol, a synthetic oestrogen used at different concentrations, while in HRT conjugated equine oestrogens, natural oestrogens (17β-oestradiol, oestrone, oestriol) or synthetic oestrogens (oestradiol valerate, benzoate, enantate, undecilate) are commonly used. Several kinds of progestagens are available and each molecule may exert
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- progesterone and progesterone like derivatives:
  - micronized progesterone
  - dehydroprogesterone
  - medrogestone
  - nomegestrol acetate

- 17α OH-progesterone derivatives:
  - medroxyprogesterone acetate
  - ciproterone acetate
  - clormadinone acetate
  - megestrol acetate

- 19 nortesterone derivatives:
  - noretisterone
  - noretisterone acetate
  - desogestrel
  - gestodene
  - norgestimate

Figure 3. Progestagen compounds used in contraceptive pills and in hormone replacement therapy (HRT).

multiple effects within the brain. Among the progestagen molecules used in oral contraceptives, it is possible to identify different types of synthetic compounds (Figure 3). Some pills contain molecules derived from the 19-nortesterone, characterized by the presence of a 17β-ethinylic group, which can be divided in two groups, the first containing 13-methylenic group (noretisterone, noretindrone, norethinodrel) and the second, 13-ethylenic group (levonorgestrel and its derivative molecules with lower androgenic activity: desogestrel, gestodene, norgestimate). Other progestins used are the 17β-OH-progesterone derivatives (ciproterone acetate) that exert anti-androgenic effects.

At present, few studies have investigated the effects of oral contraceptive treatments and, in particular, of progestagens on psychophysiological and behavioural functions. Some retrospective studies, investigating the causes of discontinuation of oral contraceptives, reported negative mood changes in ~30% of women. Women treated with low doses of progestagens experienced fewer psychophysical symptoms than those treated with higher concentrations. In treated women, symptoms develop as soon as the women start to take the combined pill and gradually increase in severity until the end of the treatment. Among the different types of progestagen used, the molecules containing the 13-ethylenic group appear to be less symptom-provoking. The derivative compounds produced after metabolization of exogenous progestagens form a major contribution to the modulation of psychophysiological function. For example, micronized progesterone given orally is metabolized to 3α-5α-OH THP and the higher circulating concentrations of this metabolite may induce sedation (Arafat et al., 1988). Experimental studies have demonstrated an anxiolytic effect of large dosages of progesterone, which is mediated by the 5α-reduced metabolites (Zwain and Yen, 1999). This effect is also found in patients affected by
premenstrual symptoms; women treated with oral micronized progesterone described beneficial effects. On the contrary, the administration of vaginal progesterone is not followed by higher concentration of metabolites in the circulation and the treatment with vaginal progesterone had no beneficial effects over placebo in patients suffering from premenstrual syndrome (Backstrom et al., 1992; Graham et al., 1992).

In HRT, different progestagen molecules are used in association with oestrogens. It is possible to associate natural progesterone or a progestin (synthetic compound with progestative functions). Among progestins used in HRT, it is possible to identify some compounds derived from progesterone and other molecules derived from 19-nortestosterone (Figure 3). The most commonly used progestrone derivatives are cyproterone acetate, medroxyprogesterone, medrogestone, and dehydrogestosterone; among the 19-nortestosterone derivatives: noretisterone, noretisterone acetate and levonorgestrel.

Some studies have investigated the effects of exogenous progestagen treatment used in post-menopausal women undergoing HRT on mood and cognitive functions. The oestro–progestagen sequential replacement therapy restores the pattern of hormonal variation during an ovulatory menstrual cycle, while oestrogen treatment alone is similar to an anovulatory cycle. Women on sequential treatments develop a cyclicity in their mood and physical signs. In many of these studies, negative effects by progesterone on the brain have been reported that produce, in some patients, a state of dysphoric mood (Hammerback et al., 1985; Magos et al., 1986). Women undergoing only oestrogen replacement therapy do not show any mood variations during the treatment.

Negative mood modification by progestagens has been demonstrated in clinical trials using different combinations of oestrogen and progestin compounds: conjugated equine oestrogens and medroxyprogesterone acetate (Sherwin, 1991), oestrogen implants and nortesterone (Magos et al., 1986), percutaneous oestradiol and lynestronol (Holst et al., 1989), and ethinyl oestradiol and levonorgestrel (Dennerstein and Burrows, 1979). These actions are probably due to the active metabolites of progesterone, e.g. allopregnanolone, 17-OH pregnanolone and 17-OH progesterone. These metabolites can be formed systemically or locally by progesterone. It is possible to speculate that progestagens and their metabolites may negatively influence mood throughout the enhancement of MAO activity and GABA inhibitory action that induce a lowering of brain excitability (Figure 2).

Several studies have focused attention on the effect of administering oestro–progestin compounds on the opioidergic system. In women, changes in the plasma β-endorphin concentration during the menstrual cycle and, in particular, the increase in circulating β-endorphin concentrations during the periovulatory days appear to be related to ovulatory function (Genazzani and Lucchesi, 1997). These data confirm the specific role of gonadal hormones in the modulation of the opioidergic system, the peak is related to ovarian function. The β-endorphin increase during the periovulatory phase seems to be related to the typical midcycle increase in plasma oestradiol concentrations (Comitini and Petraglia, 1989).

A decrease in plasma β-endorphin concentrations has been shown in post-
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menopausal women after surgical or spontaneous menopause (Linghtman and Jacobs, 1981; Genazzani and Petraglia, 1984). The decrease of plasma β-endorphin has also been related to the pathogenesis of mood, behaviour and nociceptive disturbances of post-menopausal period (McLoughlin and Grossman, 1984; Stomati et al., 1997). Oestrogen treatment ameliorates the opiateergic activity and increases circulating β-endorphin concentrations to premenopausal values. Moreover, the administration of different progestagens does not modify the positive effect of oestrogen on the opiateergic system (Stomati et al., 1997). Regarding the effects of progestins on neurovegetative symptoms and cognitive functions the few data available suggest that progestins do not modify the positive effects of oestrogen (Sherwin and Gelfand, 1989; Sherwin, 1991; Backstrom et al., 1992).

Neurosteroids

Recently, the attention focused on GABA-mediated modulation of the hypothalamic–pituitary–gonadal axis has led to the identification of the brain as a source of sex steroid hormones, named neurosteroids that bind to GABA_A receptors. The term neurosteroids has subsequently come to also include progesterone, its metabolites and other steroids produced in the brain from blood-borne precursors. The neurosteroids have a 3α-hydroxy-Δ5 structure and the first step in the synthesis of these compounds is the chain cleavage of cholesterol, involving cytochrome P-450 activity. The glial cells contain the cytochrome P-450 and are able to transform the classical steroid hormones to a variety of neuroactive compounds. Neurosteroids influence brain function via both genomic and non-genomic mechanisms; the first includes the modulation of calcium channel currents and of chloride channel opening (Palumbo et al., 1995). Electrophysiological and ligand experiments have shown that allopregnanolone, pregnanolone and allotetrahydro deoxycorticosterone act as GABA_A agonists while progesterone, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-S) exert a non-competitive antagonist action on the GABA_A receptor.

In addition, neurosteroids may modulate neural function by acting on glial cells, activating myelinization. In these complex ways, neurosteroids appear to be involved in the modulation of behavioural mechanism and psychological phenomena, e.g. the response to stressful stimuli, anxiety, seizure disorders, memory, depression and sleep. Recently, the relationship between neurosteroids and the hypothalamic–pituitary–gonadal (HPG) axis has been investigated (Bernardi et al., 1998). In female rats, brain allopregnanolone concentrations change according to the oestrous cycle: the hypothalamic allopregnanolone concentration is lower in pro-oestrous than in dioestrous or in oestrous, while the opposite is observed in the hippocampus. In addition, the modifications of hippocampal allopregnanolone concentration from prepuberty to adulthood suggests that neurosteroids may modulate the neuroendocrine changes occurring in the pubertal period. Evidence that the central injection of allopregnanolone
has an inhibitory effect on ovulation and that the antiserum to allopregnanolone enhances ovulation and sexual behaviour, support the role of allopregnanolone as an inhibitor of the hypothalamus–pituitary control of the ovulatory process. These findings suggest a role for allopregnanolone as a neuromodulator in the central mechanisms related to the HPG axis. In addition, an age-related variation of allopregnanolone in serum and in cerebral areas has been described in rats (Barbaccia and Rossetti et al., 1995). These data and the increase of cerebral allopregnanolone values under stressful conditions suggest that the stress-induced increase and the age-related decrease of allopregnanolone may have important behavioural and/or neuroendocrine consequences (Genazzani and Petraglia, 1990). Rat adrenal glands express a 5α-steroid-reductase and produce allopregnanolone, with a significant increase of the steroid adrenal contents in aged rats. The synthesis of pregnane compounds by the rat ovary has been clearly demonstrated and a novel highly-specific radioimmunoassay has been able to detect allopregnanolone in rat testis, showing a serum-parallel age-related increase (Barbaccia et al., 1995; Genazzani and Bernardi, 1999). In humans, variations in plasma allopregnanolone concentration throughout the menstrual cycle have been reported (Wang and Seippel, 1996). High concentrations were observed in the luteal phase of the menstrual cycle with controversial results on the possible involvement of allopregnanolone in premenstrual syndrome (Schmidt et al., 1994; Wang and Seippel, 1996). Recent data seem to confirm that women suffering from premenstrual syndrome have low concentrations of allopregnanolone (unpublished data). Moreover, neurosteroids may be implicated in the memory mechanism, modulating the acquisition or the loss of memory, thus suggesting that the reduced memory performances that occur in humans with ageing could be related also to a modification of the steroidogenesis. Further studies are necessary to better clarify whether additional sites of production of neurosteroids exist. The elucidation of the exact role of neurosteroids in the regulation of the reproductive function might help to understand the modification of cerebral activity, mood and sexual behaviour associated with the fluctuation of sex steroid concentrations.

Conclusions

These data support the idea that different oestrogen, progestin and androgen molecules used alone or in association exert several effects on brain functions. Gonadal hormones are of primary importance for physiological brain function, acting both on development and on the maintenance of female behaviour, cognition and reproductive function. New aspects on the complex and fascinating mechanism of brain function opened up with the finding that the CNS is also a source of neuroactive steroids. However, at present, the information on the implications of sex steroid hormones as control mechanisms of the brain function is inconclusive. Every year different kind of molecules, numerous routes and
regimens of administration are available in HRT. Further studies are required to explain the specific role of endogenous and exogenous sex steroid on the CNS.

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