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Revisiting the roles of progesterone and allopregnanolone in the nervous system: Resurgence of the progesterone receptors

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ABSTRACT

Progesterone is commonly considered as a female reproductive hormone and is well-known for its role in pregnancy. It is less well appreciated that progesterone and its metabolite allopregnanolone are also male hormones, as they are produced in both sexes by the adrenal glands. In addition, they are synthesized within the nervous system. Progesterone and allopregnanolone are associated with adaptation to stress, and increased production of progesterone within the brain may be part of the response of neural cells to injury. Progesterone receptors (PR) are widely distributed throughout the brain, but their study has been mainly limited to the hypothalamus and reproductive functions, and the extra-hypothalamic receptors have been neglected. This lack of information about brain functions of PR is unexpected, as the protective and trophic effects of progesterone are much investigated, and as the therapeutic potential of progesterone as a neuroprotective and promyelinating agent is currently being assessed in clinical trials. The little attention devoted to the brain functions of PR may relate to the widely accepted assumption that non-reproductive actions of progesterone may be mainly mediated by allopregnanolone, which does not bind to PR, but acts as a potent positive modulator of γ-aminobutyric acid type A ($GABA_A$) receptors. The aim of this review is to critically discuss effects of progesterone on the nervous system via PR, and of allopregnanolone via its modulation of $GABA_A$ receptors, with main focus on the brain.

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Abbreviations: ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; CNS, central nervous system; 5α-DHP, 5α-dihydroprogesterone; EAE, experimental autoimmune encephalomyelitis; $GABA_A$ receptors, γ-aminobutyric acid type A receptors; GC/MS, gas chromatography/mass spectrometry; HRT, hormone replacement therapy; 3α-HSD, 3α-hydroxysteroid dehydrogenase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; LPC, lysophosphatidylcholine; MBP, myelin basic protein; MCAO, middle cerebral artery occlusion; mPR, membrane progesterone receptors; nM, nanomolar; NP-C, Niemann-Pick type C disease; OPC, oligodendrocyte progenitor cell; P0, peripheral myelin protein zero; PMP22, peripheral myelin protein-22; PNS, peripheral nervous system; PR, progesterone receptors; PR-A, progesterone receptor isoform A; PR-B, progesterone receptor isoform B; PRE, progesterone response element; RIA, radioimmunoassay; SRC-1, 2, 3, steroid receptor coactivator-1,2,3; Src kinases, proto-oncogene tyrosine-protein kinases; TBI, traumatic brain injury; VMN, ventromedial nuclei of the hypothalamus; VTA, ventral tegmental area.

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1. Introduction: historical background

The brain is a major target of progesterone, and the hypothalamus was the first region where progesterone receptors (PR) were localized. In the early 1970s, the uptake of tritium ([^{3}H])-labeled progesterone by the nuclei of hypothalamic neurons was demonstrated by autoradiography in the guinea pig, suggesting a direct action of the hormone on neural cells. Moreover, pretreating the animals with estradiol was shown to enhance the nuclear uptake of radioactivity (Sar and Stumpf, 1973). At this time, it was already known that both hypothalamus and pituitary gland are targets for the ovulation-blocking actions of progestogens (Kanematsu and Sawyer, 1965). However, the study of brain PR remained elusive at the beginning, as binding of natural progesterone to its receptors was found labile, thus precluding the use of standard binding techniques. This changed with the advent of [^{3}H]promegestone (R5020), a highly potent synthetic 19-norpregnane derivative. Promegestone indeed binds to PR with high selectivity and affinity, allowing the characterization of PR binding in progesterone target tissues in relation to biological responses (Raynaud and Ojasoo, 1984). Within the rat hypothalamus, binding studies with [^{3}H]promegestone demonstrated estradiol-inducible PR, and it was shown that their upregulation is necessary for the activation of female reproductive behavior (Blaustein and Wade, 1978; MacLusky and McEwen, 1978; Moguilewsky and Raynaud, 1977, 1979b; Parsons et al., 1980).

The early binding studies also revealed that within the brain, PR expression is not limited to the hypothalamus, but that they are widely distributed throughout the brain and present in both cerebral cortex and subcortical regions. However, much lower levels of PR were found outside the hypothalamus, and they were not inducible by estrogen within many regions (MacLusky and McEwen, 1978; Parsons et al., 1982). Moreover, PR are also difficult to detect by immunohistochemistry at the light microscopic level in extra-hypothalamic regions of the adult rodent brain (Lopez and Wagner, 2009; Quadros et al., 2007, 2008; Warembourg et al., 1986). There may be two main reasons for the difficulty in studying PR outside the hypothalamus. First, PR are strongly induced within hypothalamic neurons by estrogen treatment, but only modestly or not at all in other brain regions. Second, whereas hypothalamic PR show a strong nuclear localization, allowing their easy detection, PR in neurons outside the hypothalamus are also located in extra-nuclear sites, as demonstrated recently by immunoelectron microscopy. This study indeed revealed abundant PR labeling within axons, dendrites and at the level of synapses (Waters et al., 2008). Already an earlier study using conventional immunohistochemistry had reported the presence of both PR and estrogen receptors in dendrites and axon terminals (Blaustein et al., 1992). These findings are consistent with expression studies showing elevated expression of PR mRNA outside the hypothalamus (Guerra-Araiza et al., 2001, 2003; Hagihara et al., 1992; Intlekofer and Petersen, 2011; see also the nuclear receptor expression websites NURSA and MousePat). Obviously, in neuronal compartments far distant from the nucleus, PR would not be expected to act as transcription factors, but they could instead influence neurotransmission, possibly by interacting with membrane proteins (see Section 4). It is interesting to note that a subcellular distribution in axons and dendrites has also been reported for the androgen receptor in neurons outside the hypothalamus. It was moreover shown that the cerebral cortex, and not the hypothalamic and limbic nuclei involved in the control of reproductive functions, contains the highest density of androgen receptor expressing cells (Doncarlos et al., 2003, 2006).

In this review, the term "progesterone receptors" and the abbreviation PR refer to the so-called "classical" intracellular receptors, without distinction between the two isoforms PR-A and PR-B, which are both transcribed from a single gene and also expressed in the brain (see Section 5). The term PR does not include here the multiple membrane receptors of progesterone, which have been identified more recently. Their biological significance is indeed beyond the scope of this review and has been extensively discussed elsewhere (Brinton et al., 2008; Peluso et al., 2012; Thomas, 2008; Thomas and Pang, 2012; Wendler et al., 2012).

Since the demonstration of PR in the brain, research has largely focused on the reproductive functions of hypothalamic PR, and the extra-hypothalamic receptors have largely remained unexplored (Levine et al., 2001; Mani and Portillo, 2010; Mani et al., 1994). Only a few studies have raised the possibility that brain PR outside the hypothalamus may play a wider role in the regulation of neuron activity and brain functions extending beyond reproduction (Ghoumari et al., 2003; Waters et al., 2008; Woolley and McEwen, 1993; Wu et al., 2006). However, within the spinal cord and peripheral nerves, PR have previously been proposed to play an important role in neuroprotective and regenerative mechanisms (Chan et al., 2000; Koenig et al., 1995; Labombarda et al., 2003).

The lack of interest in the functional significance of PR outside the hypothalamus, in spite of the multiple effects which progesterone exerts in the brain, cannot only be explained by their apparently lower abundance. A main reason may be that concomitantly to studies on the reproductive functions of hypothalamic PR, there has been an important line of research concerning the anesthetic, anxiolytic, analgesic and anticonvulsant actions of progesterone, which are mainly mediated by its neuroactive metabolite allopregnanolone. All started in the early forties, when Hans Seyle reported that high doses of progesterone and some of its metabolites induce anesthesia in rats (Seyle, 1941, 1942). This observation was the demonstration that steroids can very rapidly modulate brain excitability, and it led to the development of water-soluble synthetic steroidal anesthetics, which were clinically used during the seventies. For their design, attention was focused on metabolites of progesterone which were more potent than progesterone itself (Gyermek and Soyka, 1975). A therapeutically efficient mixture with the brand name Althesin was composed of alphaxolone (3α-hydroxy-5α-pregnane-11,20-dione), a synthetic derivative of the natural progesterone

metabolite allopregnanolone (3α-hydroxy-5α-pregnane-20-one or 3α,5α-tetrahydroprogesterone), its 21 acetoxy ester and Cremophor, used as a solvent and emulsifying agent (Child et al., 1971). This product has been withdrawn from the market because of adverse effects, probably caused by the solubilizing agent. However, in veterinary practice, alphaxolone continues to be used as an anesthetic for dogs and cats under the tradename Alfaxan (Muir et al., 2008, 2009).

An important step toward the elucidation of the mechanism of action of alphaxolone was the observation that it potently enhances the function of the major inhibitory receptors in the brain, the γ-aminobutyric acid type A ($GABA_A$) receptors (Harrison and Simmonds, 1984). This observation evidently raised the question of the actions of allopregnanolone, the natural metabolite of progesterone from which alphaxolone was derived. In the seventies, Karavolas and collaborators had indeed shown that progesterone is converted to 5α-dihydroprogesterone (5α-DHP) and allopregnanolone within the rat hypothalamus and pituitary gland (Cheng and Karavolas, 1973; Karavolas et al., 1976). In 1986 came the demonstration that both allopregnanolone (3α,5α-tetrahydroprogesterone), as well as 3α,5α-tetrahydrodeoxycorticosterone, are natural positive modulators of neuronal $GABA_A$ receptors (Majewska et al., 1986). This finding provided a mechanistic insight into the rapid psychopharmacological actions of progesterone and its metabolites, and since then, there has been much interest in the anxiolytic, antidepressant, anesthetic, anticonvulsant and analgesic effects of allopregnanolone (Belelli and Lambert, 2005; Frye, 2008; Reddy, 2010; Rupprecht, 2003; Rupprecht et al., 2010). However, the location of a steroid binding site on $GABA_A$ receptors remained an enigma for an additional 20 years. It was only in 2006 that allopregnanolone was shown to regulate the activity of $GABA_A$ receptors through two discrete binding sites, located within the transmembrane domains of the α- and β-receptor subunits, and distinct from the benzodiazepine binding site (Hosie et al., 2006). The proposed model predicted a canonical binding site important for both steroid activation of $GABA_A$ receptors (in the absence of GABA) and their potentiation (in the presence of GABA), located on the α-subunit, and a second site critical for receptor activation at the α–β subunit interface. Importantly, these binding sites appear to be conserved in the different isoforms of both α- and β-receptor subunits, explaining why steroids modulate the activity of a broad variety of $GABA_A$ receptors (Hosie et al., 2007).

Two major lines of research concerning progesterone effects on the brain can thus be identified: one concerning its reproductive functions mediated by hypothalamic PR and a second line studying its psychopharmacological actions, involving the modulation of $GABA_A$ receptors by allopregnanolone. An additional area of research started in the nineties with the discovery that progesterone and allopregnanolone have neuroprotective effects and promote nerve regeneration and myelination. Two landmarks were the observations that progesterone treatment protects against traumatic brain injury (TBI), and that progesterone plays a key role in the formation of new myelin sheaths after nerve injury (Koenig et al., 1995; Roof et al., 1993, 1994). Subsequently, neuroprotective effects of progesterone and allopregnanolone have been demonstrated in many injury models, including cerebral ischemic stroke (Gibson and Murphy, 2004; Jiang et al., 1996; Sayeed et al., 2006), excitotoxic damage of hippocampal neurons (Ciriza et al., 2004) and traumatic spinal cord injury (De Nicola et al., 2009), and in mouse models of spontaneous spinal motoneuron degeneration, Niemann-Pick type C disease and Alzheimer's disease (Gonzalez Deniselle et al., 2001; Griffin et al., 2004; Wang et al., 2008, 2010b). Most of these studies proposed the neuroprotective effects of progesterone to be mediated by allopregnanolone, neglecting the possibility of an important role of brain PR. This explains why efforts are underway to develop synthetic analogs of allopregnanolone with neuroprotective efficacy, in addition to their anxiolytic and anti-seizure activities (MacNevin et al., 2009; Mellon et al., 2008; Reddy, 2010; Xilouri et al., 2007).

However, the view that the protective and regenerative effects of progesterone in the brain may be primarily mediated by allopregnanolone has recently been challenged by the observation that PR play a key role in the viability of neurons after ischemic stroke and in the remyelination of axons after a demyelinating lesion (Hussain et al., 2011; Liu et al., 2012). The recognition of PR as a major player in progesterone neuroprotection has of course important therapeutic implications, as it opens the way for the use of synthetic progestins, designed to selectively target PR, to promote neuroprotection and myelin repair. Clarifying the signaling mechanisms of progesterone in the brain has become an urgent problem in light of the already completed and ongoing clinical trials aimed at testing the beneficial effects of progesterone in patients with TBI (Wright et al., 2007; Xiao et al., 2008; see also the websites of the ongoing phase 3 SyNAPSe and ProTECT III trials), multiple sclerosis (Vukusic et al., 2009) and carpal tunnel syndrome (Milani et al., 2010). Endogenous levels of progesterone were also found to correlate positively with factors predicting better prognosis and survival of patients with amyotrophic lateral sclerosis (ALS) (Gargiulo Monachelli et al., 2011).

2. A reappraisal of steroid terminology

Neurologists and neurobiologists are often not familiar with the diversity of steroid hormones, their various mechanisms of actions and their multiple effects within the nervous system. In neurological practice, the term "steroids" commonly refers to synthetic corticosteroids (corticoids), as for example methylprednisolone, prednisone or dexamethasone, used for anti-inflammatory therapy in disorders such as multiple sclerosis and chronic inflammatory demyelinating polyneuropathy (Hughes and van Doorn, 2012; Myhr and Mellgren, 2009). The use of corticosteroids after traumatic injuries has become controversial. Although their early administration at a high-dose is still a standard of care in acute traumatic spinal cord injury (Bracken, 2012), their use for the treatment of TBI has been reconsidered after the outcomes of the CRASH trial, an international multicenter and placebo-controlled trial involving about 20,000 patients. In this trial, infusion of methylprednisolone for two days after TBI was indeed shown to significantly increase the risk of death (Edwards et al., 2005). This type of "steroid treatment" has evidently nothing to do with the administration of progestogens after brain and spinal cord injury.

Neurobiologists on the other hand usually consider steroids as hormones of reproduction (progestogens, estrogens and androgens), metabolism and adaptation to stress (glucocorticoids) or salt and water balance regulation (mineralocorticoids). Evidently, the five different classes of steroid hormones are critically involved in the regulation of these functions, but their roles go far beyond them, as will be documented in this review by the pleiotropic effects of progesterone and allopregnanolone in the nervous system.

The expression "steroid hormone" comprises two terms. Readers should be reminded here that the chemical definition of a "steroid" is a molecule with a core carbon skeleton, known as the sterane nucleus and composed of 3 cyclohexane rings (designated as rings A, B and C) and one cyclopentane ring (the D ring). The 17 carbon atoms of this nucleus are numbered from C1 to C17, and steroids vary by the functional groups attached to the skeleton and by the oxidation state of the four rings, resulting in small molecules with very different properties and biological activities (Fig. 1). A wide variety of steroids exists, including those with their 6 carbon

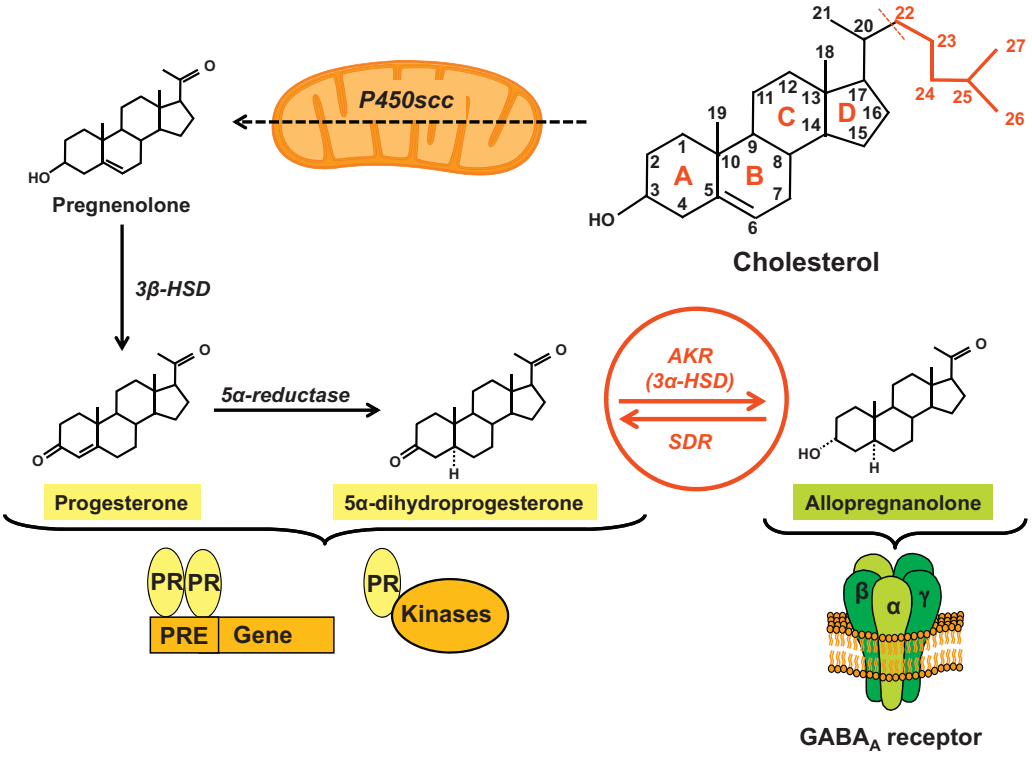

Fig. 1. Biosynthetic pathway of progestogens. The cholesterol molecule shows the numbering of the 27 carbons of the sterane nucleus, its functional groups and the 6 carbon side-chain (in red) which is characteristic of sterols. Cholesterol is converted to pregnenolone inside the mitochondria by the side chain cleavage cytochrome P450scc. Pregnenolone is then converted to progesterone by the 3β-hydroxysteroid dehydrogenases (3β-HSD). The conversion of progesterone to 5α-dihydroprogesterone is catalyzed by one of the two 5α-reductase isoforms. Both progesterone and 5α-DHP bind to the classical intracellular progesterone receptors (PR), which regulate gene transcription within the cell nucleus or interact with kinases and components of intracellular signaling pathways within extra-nuclear compartments. 5α-DHP can be metabolized to allopregnanolone (3α,5α-tetrahydroprogesterone) by aldo-keto reductases (ARK; 3α-HSD = 3α-hydroxysteroid dehydrogenase). Because of its hydroxyl group at C3, allopregnanolone has no affinity for the intracellular PR, but is a potent allosteric modulator of GABA$_A$ receptors. However, allopregnanolone can activate gene transcription via PR after being converted back to 5α-dihydroprogesterone by short-chain dehydrogenases/reductases (SDR).

side-chain (sterols, cholesterol and oxysterols), the bile acids, the secosteroids with a broken B-ring (vitamin D) and the different classes of the so-called steroid hormones. They are synthesized after removal within the mitochondria of the cholesterol side-chain by the P450 side-chain cleavage cytochrome (P450scc), encoded by the unique *CYP11A1* gene. The term "homone" has been coined by Ernest Starling during one of his lectures in 1905 to define chemical messengers which "... *have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream* ..." (Henderson, 2005; Starling, 1905). It thus refers to the so-called endocrine mode of signaling.

However, the steroidogenic endocrine glands, gonads and adrenal glands, are not the only source of steroids. Indeed, the nervous system is another important site of steroid formation and metabolism, and both neurons and glial cells can synthesize progesterone and allopregnanolone from circulating precursors and even *de novo* from cholesterol (Baulieu, 1997; Mellon and Vaudry, 2001; Schumacher et al., 2007a). To refer to their site of synthesis, the term "*neurosteroid*" has been coined for steroids that are synthesized within the nervous system, where they act via autocrine, paracrine and possibly also intracrine signaling mechanisms (Baulieu, 1981; Baulieu et al., 2001). Thus, if progesterone is synthesized by an endocrine gland, it acts as a steroid hormone, whereas progesterone synthesized in the brain can be considered as a neurosteroid. The terms "neurosteroid" and "neuroactive steroids" should not be used in an interchangeable manner, as the latter corresponds to a functional concept and refers to natural or synthetic steroids which can rapidly alter the excitability of neurons by binding to membrane-bound receptors such as those for inhibitory or excitatory neurotransmitters (Paul and Purdy, 1992). For example, allopregnanolone can be considered as a neuroactive steroid as it modulates the activity of GABA$_A$ receptors, and also as a neurosteroid when it is synthesized within the nervous system.

There is also considerable confusion in the literature about the terms progesterone, progestagens, progestogens and progestins. The term progesterone should only be used for the natural hormone, also qualified as bioidentical, and never as a generic one to design different natural or synthetic compounds. The functional terms "progestogens" (adopted in this review) or "progestagens" refer to natural or synthetic molecules with progestational activity, those which prepare the uterus for pregnancy. The term "progestin" is used here for synthetic compounds designed to target the PR (Schumacher et al., 2007a; Stanczyk et al., 2013). It is important to be aware that progestins belong to different classes with sometimes very different pharmacological properties and modes of action (Schumacher et al., 2008; Sitruk-Ware, 2008; Stanczyk et al., 2013).

3. Biosynthetic pathway of progesterone and allopregnanolone

Like all steroid hormones, progesterone is synthesized from cholesterol, and its formation involves two successive enzymatic steps: the conversion of cholesterol to pregnenolone inside the mitochondria by cytochrome P450scc and then the conversion of pregnenolone to progesterone by a 3β-hydroxysteroid dehydrogenase (3β-HSD), located either in the mitochondria or in endoplasmic reticulum membranes depending on the steroidogenic cell type (Cherradi et al., 1995; Luu et al., 1989) (Fig. 1). As cholesterol is a very hydrophobic molecule, it can neither freely

move through the aqueous spaces of the cell, nor enter the mitochondria by simple diffusion, but requires carrier proteins. The translocation of cholesterol inside the mitochondria involves a protein complex named the "transduceosome" (Midzak et al., 2011). Two important components of this complex are the translocase 18 kDa (TSPO), the former peripheral benzodiazepine receptor, and StAR. The TSPO mediated translocation of cholesterol from the outer to the inner mitochondrial membrane is the rate-limiting step in the synthesis of pregnenolone. By increasing the intra-mitochondrial transport of cholesterol, agonist ligands of TSPO stimulate steroid formation. Three-dimensional models suggest that TSPO may function as a channel, accommodating a cholesterol molecule in the space delineated by five transmembrane domains (Rupprecht et al., 2010). The mechanisms by which the mitochondria-targeted protein StAR drives the transfer of cholesterol and increases steroidogenesis are less well understood. It has been proposed that StAR may transport cholesterol to the mitochondria. Another model suggests that StAR may drive steroid formation by functioning as a shuttle, moving cholesterol from the outer to the inner mitochondrial membrane (Rone et al., 2009; Midzak et al., 2011).

The 3β-HSD enzymes, which exist under several isoforms, catalyze two reactions at distinct active sites: the dehydrogenation of the hydroxyl group at carbon 3 (C3) and the isomerization of the double bound between C5 and C6 to a double bound between C4 and C5. Multiple 3β-HSD isoforms have been identified in different species: six in mice, four in rats and only two in humans (Simard et al., 2005). Unfortunately, there is a problem of nomenclature, since the different 3β-HSD isoforms have been numbered according to the chronology of their discovery, and the isoforms of different species do not correspond by number. For example, in humans, the type 1 isoform accounts for 3β-HSD activity in placenta, whereas the type 2 isoform is predominantly expressed in gonads, adrenal glands and brain (Inoue et al., 2002; Simard et al., 2005). Deficiency of 3β-HSD type 2 is at the origin of a rare form of congenital adrenal hyperplasia (Krone and Arlt, 2009; Simard et al., 2002). On the contrary, in rats and mice, the type 1 isoenzyme is expressed in gonads and adrenal glands and also in brain, where it is largely distributed (Guennoun et al., 1995; Simard et al., 2005).

Progesterone can be metabolized to 5α-DHP by two isoforms of steroid 5α-reductases, which irreversibly reduce the double bound between C4 and C5 by adding hydrogens. The type 1 enzyme is widely expressed in the rat brain at all stages of development, whereas the type 2 enzyme shows a more restricted distribution (Melcangi et al., 1998; Patte-Mensah et al., 2004a). Both progesterone and 5α-DHP are ligands of the intracellular PR and are regulators of gene transcription (Rupprecht et al., 1993). However, within the uterus, 5α-DHP has no progestational activity, as it is rapidly metabolized, and the 5α-reductase pathway has been proposed to reduce the pregnancy maintaining effect of progesterone (Byrns, 2013; Kubli-Garfias et al., 1979; Saffran et al., 1978). Conversely, in the brain, 5α-DHP may be an important biologically active metabolite of progesterone and involved in the regulation of neuroendocrine functions (Beyer et al., 1995; Karavolas et al., 1976). Nevertheless, after transient transfection of PR expression vectors into a human neuroblastoma cell line, 5α-DHP showed high affinity only for the chicken PR, whereas its activity at the level of the human PR was much less pronounced (Rupprecht et al., 1993). Thus, the functional significance of 5α-DHP in neural cells requires to be clarified.

5α-DHP is further converted to allopregnanolone by NADPH-dependent cytosolic aldo-keto reductases (AKR). In contrast to progesterone and 5α-DHP, allopregnanolone does not bind to PR, but as already mentioned, is a positive modulator of $GABA_A$ receptors (Belelli and Lambert, 2005; Gee et al., 1988; Rupprecht et al., 1993). Whereas rats only have a single ARK isoform (AKR1C9), also named 3α-hydroxysteroid dehydrogenase (3α-HSD) as the enzyme specifically converts the 3-ketosteroid 5α-DHP to the 3α-hydroxysteroid allopregnanolone, multiple and less selective ARK isoforms are present in humans and mice (Ishikura et al., 2004; Penning et al., 2003). Particularly important for our discussion of the respective roles of PR and allopregnanolone signaling in the brain is the fact that allopregnanolone can be converted back to 5α-DHP by NAD^+-dependent membrane-associated short-chain dehydrogenases/reductases (SDRs), acting *in vivo* as 3α-hydroxysteroid oxidases (Belyaeva et al., 2007; Chetyrkin et al., 2001; Penning, 2011) (Fig. 1). Conversion back to 5α-DHP is indeed a mechanism by which allopregnanolone can activate PR-dependent gene transcription (Rupprecht et al., 1993). The conversion of 5α-DHP to epiallopregnanolone (3β,5α-tetrahydroprogesterone), which is inactive and can even antagonize the effects of allopregnanolone at $GABA_A$ receptors, is less well characterized (Backstrom et al., 2005). Allopregnanolone can be epimerized to epiallopregnanolone by 3(α→β) hydroxysteroid epimerase activity. This reaction most likely involves two successive enzymatic steps: the oxidation of the 3α-hydroxyl group followed by the reduction of the 3-ketone group to a 3β-hydroxyl group (Belyaeva et al., 2007; Higashi et al., 2004).

Although the present review will be limited to the above described metabolic pathways of progesterone, it should be acknowledged that there exist many others, which are part of a metabolic network. For example, progesterone can be converted to 5β-dihydroprogesterone or to 20α-dihydroprogesterone, which in turn are metabolized. Moreover, these different pathways are interdependent. For example, blocking the stress-induced increase in brain allopregnanolone by the administration of the 5α-reductase inhibitor finasteride promotes the 20α-metabolic pathway (Mukai et al., 2008). However, the biological significance of all these progesterone metabolites remains unknown, and they may either belong to inactivation pathways of the hormone, or they may have their own biological activity (Choi et al., 2008; Pasqualini and Chetrite, 2008; Wiebe, 2006).

4. Progesterone receptor signaling: up-to-date knowledge

In reproductive tissues, the major biological effects of progesterone on its target cells are mediated by two PR isoforms, which are encoded by a single gene located on human chromosome 11 and on mouse chromosome 9. Progesterone receptor-A (PR-A) and progesterone receptor-B (PR-B) are indeed transcribed from two distinct promoter regions of a single gene (Conneely et al., 1989; Kastner et al., 1990; Kraus et al., 1993). Importantly, both promoters of the human *PR* gene are activated by estrogens, consistent with the observation that PR expression is strongly upregulated by estradiol in uterus, mammary glands, pituitary glands and hypothalamus (Graham and Clarke, 1997; Kastner et al., 1990; Scott et al., 2002). In fact, the proximal promoters controlling respectively PR-A and PR-B transcription contain estrogen response elements (ERE) to which estrogen receptors bind, and cells containing estrogen-inducible PR generally express estrogen receptors (Jacobsen and Horwitz, 2012). The more recent identification of estrogen response elements far removed from the transcription start sites of PR-A and PR-B strongly suggests that long-range regulation of the *PR* gene by estradiol also may occur (Boney-Montoya et al., 2010). In rabbits, an ERE was shown to also mediate progesterone-dependent down-regulation of PR (Savouret et al., 1991).

In common with the other members of the steroid receptor superfamily, PR are composed of four functional domains: an N-terminal regulatory domain, a DNA binding domain (DBD) comprising two highly conserved zinc fingers, hinge region and

a C-terminal ligand binding domain (LBD), which is also involved in receptor dimerization. In addition, there are specific sequences to which nuclear coregulators bind. They include both transcription activation function (AF) domains and inhibition function (IF) domains (Wardell et al., 2002). Within the nucleus, PR bind to specific DNA binding sites, named progesterone response elements (PRE) and regulate the transcription of progesterone-sensitive genes. The binding of coactivators to the AF plays a key role in the transcriptional activity of PR, as the receptors themselves do not possess enzymatic activities necessary for chromatin remodeling (Han et al., 2007; Scarpin et al., 2009). Importantly, the recruitment of coactivators is a rate-limiting step in steroid receptor-mediated gene transcription. As a consequence, the transcriptional activity of a specific nuclear receptor can repress the transcriptional activity of another receptor through the squelching of coactivators (Meyer et al., 1989; Onate et al., 1995; Rosenfeld et al., 2006). This also means that the response to a hormone like progesterone is not only dependent on the presence of sufficient levels of PR, but also on the availability of coactivators. Since the discovery of the first nuclear receptor coactivator, named steroid receptor coactivator-1 (SRC-1), over 350 coregulatory proteins have been identified, including coactivators and corepressors, and we are only starting to appreciate their complexity (Amazit et al., 2011; Kato et al., 2011; Li and O'Malley, 2003; York and O'Malley, 2010). Moreover, their functions go well beyond the role of transcriptional adaptors: they may contribute to the cell- and tissue-specific actions of steroid receptor ligands and they transduce multiple signaling pathways (Abdel-Hafiz et al., 2009; Wu et al., 2005).

According to the classical view, gene transcription is activated by PR dimers bound to palindromic PRE. However, this model needs to be reevaluated on the basis of recent evidence suggesting that PRE half-sites may be more abundant than palindromic PRE, and that PR monomers may even be more efficient transactivators than PR dimers (Jacobsen et al., 2009; Jacobsen and Horwitz, 2012). Such a signaling mechanism is further supported by thermodynamic studies showing more favorable energies for the binding of PR monomers to responsive DNA elements when compared to PR dimers (Connaghan-Jones and Bain, 2009).

It is now recognized that PR interact with chromatin in a highly dynamic manner, dependent on chromatin structure, chaperone proteins, the proteasome and the presence of other transcription factors (Grontved and Hager, 2012). The transcriptional activity of the ligand-bound PR involves chromatin remodeling and crosstalk with signaling pathways initiated within the cytoplasm (Al-Sabbagh et al., 2012; Beato and Vicent, 2012; Hagan et al., 2012; Jones et al., 2006; Khan et al., 2011). This crosstalk results in post-translational modifications of PR, including its phosphorylation, sumoylation, acetylation and ubiquitination, which not only influence its transcriptional potency, but may also contribute to its selective interactions with promoter regions (Abdel-Hafiz et al., 2009; Chauchereau et al., 2003; Daniel et al., 2010; Khan et al., 2011; Rosenfeld et al., 2006; Yang and Seto, 2008). There is also evidence that the fine tuning of gene regulation by progesterone may involve microRNAs mediating gene silencing at the post-transcriptional level. However, this field of investigation is relatively new and unexplored (Cochrane et al., 2012).

Another major breakthrough came from real-time kinetic analysis of steroid receptor interactions with their DNA response elements. They have revealed that the interaction of PR and other steroid receptors with chromatin is not as stable as previously thought, supposedly lasting for minutes and even hours. In fact, the receptors undergo very rapid exchanges, on a time scale of seconds, between the nucleoplasm and gene promoters (Hager et al., 2009; Rayasam et al., 2005). Real-time dynamics of the rapid cycling of nuclear receptors on chromatin has been particularly well studied for the glucocorticoid receptor (GR). For this receptor, cyclic recruitment by chromatin was shown to be crucial for optimal neuronal and behavioral responsiveness to rapidly fluctuating glucocorticoid levels (Conway-Campbell et al., 2012; Lightman and Conway-Campbell, 2010).

Understanding the mechanisms by which PR signaling elicits multiple effects within target tissues requires the identification of its target genes. Even in classical targets such as the uterus and mammary glands, precise transcriptional responses to progesterone still remain to be determined. A reason for this gap is the high variability of PRE sequences to which PR bind (Rubel et al., 2012) and the multiple ways PR can interact with chromatin. In fact, PR not only bind DNA directly, but they also interact with other nuclear factors such as AP1, SP1 and STATs (Beguelin et al., 2010; Faivre et al., 2008; Owen et al., 1998; Stoecklin et al., 1999). As a consequence of this complexity, *in silico* prediction of functional PRE remains insufficient. The use of new technologies for studying physical interactions between chromatin and transcription factors, such as chromatin immunoprecipitation followed by massively parallel sequencing, named ChIP-sequencing, has allowed a major step forward in the identification of progesterone target genes. In the mouse uterus, the genome-wide profiling of PR binding with the use of this technology has revealed thousands of PR-binding sites: more than 6000 in ovariectomized mice and more than 18,000 after exposure of the animals to progesterone (Rubel et al., 2012).

The ChIP-sequencing technology, together with other new genomic approaches with an unprecedented resolution, such as genome wide analysis of DNase I hypersensitivity sites by deep sequencing (DHS-seq) and cutting edge chromatin accessibility techniques, have also revealed that the ability of steroid receptors to engage chromatin is determined to a great extent by preestablished accessible chromatin states (Grontved and Hager, 2012; John et al., 2011). Chromatin organization is now recognized as a major contributor to the transcriptional specificity of steroid receptors and their cell-and tissue-specific signaling. Importantly, the accessibility of the genome to steroid receptors may be established during development and may involve enduring epigenetic shaping of steroid receptor functions (Grontved and Hager, 2012; Meaney and Ferguson-Smith, 2010). According to a challenging view, the transcriptional activity of nuclear receptors may in turn result in epigenetic chromatin reorganization (Kato et al., 2011). A seminal example of epigenetic influences on steroid receptor signaling is the modification of the hippocampal glucocorticoid receptor (GR) gene promoter in offspring by maternal care. Changes in the epigenetic status of GR promoter involve DNA methylation, the acetylation of histone tails and altered transcription factor binding (Weaver et al., 2004). In the hypothalamus, the promoters of the genes encoding PR and estrogen receptors also show epigenetic changes which are established during development in a sex-specific manner (Nugent and McCarthy, 2011; Schwarz et al., 2010).

Concerning the two PR isoforms, the actions of PR-A and PR-B are remarkably divergent and target distinct gene networks in progesterone-responsive cells, in spite of their similar hormone- and DNA-binding affinities (Al-Sabbagh et al., 2012; Conneely et al., 2002; Jacobsen and Horwitz, 2012; Richer et al., 2002). There are even a few examples of gene promoters on which PR-A and PR-B have opposite effects. This is the case for the uteroferrin, catechol-O-methyltransferase, human gonadotropin releasing hormone receptor and corticotrophin-releasing hormone genes (Cheng et al., 2001; Jacobsen and Horwitz, 2012; Ni et al., 2004; Tsuchiya et al., 2003; Zhang et al., 2003). How the two PR isoforms exert their specific transcriptional effects remains to be solved, but it has been proposed that nuclear coregulator proteins and transcription factors flanking the PRE may contribute to PR isoform specificity (Jacobsen and Horwitz, 2012). Studies from

isoform-specific knockout-mice have shown that PR-B is necessary for normal mammary gland development, while PR-A is required for uterine functions (Conneely et al., 2002; Mulac-Jericevic and Conneely, 2004).

This short overview shows that our understanding of the mechanisms by which PR and other nuclear receptors regulate gene expression is progressing rapidly, and we are becoming increasingly aware of the great complexity of hormone-sensitive networks. Work over the past few years has established the importance of nuclear coregulator proteins, and that PR can also bind as monomers to DNA response elements, sometimes located far away from the transcription start site of progesterone-sensitive genes. Particularly important was the observation that PR and other steroid receptors interact with chromatin in a highly dynamic manner, influenced by their post-transcriptional modifications and the dynamic as well as epigenetic changes in chromatin structure. Genome-wide profiling of PR binding by technologies such as ChIP-sequencing has revealed an unexpectedly large number of potential progesterone target genes within hormone-sensitive tissues. In contrast, our knowledge of the respective functions of the PR-A and PR-B isoforms remains limited.

5. Progesterone receptors are not only nuclear transcription factors

As discussed above, PR in neurons outside the hypothalamus are often located in axons, dendrites and at the level of synapses, thus far away from the nucleus. These receptors may directly interact with signaling complexes associated with the cell membrane. It is important to point out that we are discussing here interactions of the classical intracellular PR with proteins located at the inner side of the plasma membrane, such as kinases, and not the signaling mechanisms of the more recently identified transmembrane domain receptors of progesterone.

A first example of extra-nuclear PR signaling mediated via G protein subunits had already been reported more than 35 years ago. It was observed that meiotic progression in Xenopus oocytes involves membrane actions of progesterone, leading to a rapid increase in intracellular Ca^{2+}, inhibition of the adenylate cyclase/protein kinase A system and activation of the mitogen-activated protein kinase (MAPK) cascade (Baulieu et al., 1978; Godeau et al., 1978). Much later, it was shown that the membrane actions of progesterone involve the amphibian homolog of the mammalian intracellular PR, which mediates rapid effects of progesterone after its translocation to the cell membrane (Bagowski et al., 2001; Bayaa et al., 2000; Maller, 2001).

We now know that PR have multiple protein kinase-interacting and scaffolding domains, and that they can directly bind to the SH3 domain of proto-oncogene tyrosine-protein kinases (Src kinases), causing rapid activation of the growth factor-dependent MAPK pathway (Boonyaratanakornkit et al., 2001, 2008; Hagan et al., 2012). Whether the interaction between PR and Src kinases occurs in the cytoplasm or at the level of the plasma membrane remains to be determined. These kinases indeed reside in cytoplasmic sites and are translocated to the cell membrane upon activation. PR can also directly associate with cytoplasmic kinases, as has been demonstrated for MAPK, phosphatidylinositol 3-kinase (PI3K) and cyclin-dependent kinases (CDK) (Bagowski et al., 2001; Faivre et al., 2005; Narayanan et al., 2005). The PR-dependent activation of cytoplasmic protein kinases may contribute to the phosphorylation of PR residing in the nucleus, allowing their optimal transcriptional activity. There exists indeed a cross-talk between progesterone-dependent extra-nuclear kinase activation and intranuclear transcription. In addition, PR-activated kinase pathways may regulate the transcription of genes which are not direct targets of progesterone (Boonyaratanakornkit et al., 2008; Faivre and Lange, 2007; Lange et al., 2007).

However, PR-activated kinases not only target transcriptional events, they can also rapidly affect extra-nuclear targets (Lange et al., 2007). For example, in breast cancer cells, binding of progesterone to PR activates the RhoA/Rho-associated kinase (ROCK-2) cascade, leading to modifications in the actin cytoskeleton and regulating the focal adhesion kinase (FAK) via the c-Src/PI3K/Akt pathway, resulting in the formation of adhesion complexes at the level of the cell membrane (Fu et al., 2008, 2010). This type of extra-nuclear PR signaling may play a particularly important role in compartments of the nervous system, where the receptors are located far away from neuronal cell bodies.

There is now compelling evidence that all steroid receptors can mediate extra-nuclear steroid actions. A mechanism driving steroid receptors to the plasma membrane has been identified for the α-isoform of the estrogen receptor (ERα). Attachment of palmitic acid to cysteine 447 of the human ERα ligand-binding domain or to cysteine 451 in mice was shown to be required for translocation of the receptor to the plasma membrane, its interaction with caveolin-1 and activation of the ERK and PI3K/Akt signaling cascades (Acconcia et al., 2005). Palmitoylation is a conserved mechanism, probably involved in the translocation of all steroid receptors to the cell membrane. In contrast to steroid receptors located at the cell membrane, nuclear receptors are not palmitoylated, supporting the idea that palmitoylation drives the steroid receptors to the plasma membrane (Levin, 2011; Pedram et al., 2007). Interestingly, palmitoylation preferentially occurs on ERα monomers in the absence of ligand. Estradiol binding then rapidly promotes dimerization of the membrane receptors and a conformational change for rapid signaling via G protein activation (Razandi et al., 2004). Two palmitoylacyltransferases for sex steroid receptors have been recently identified (DHHC-7 and DHHC-21), and their knockdown has been shown to inhibit the palmitoylation of PR, its translocation to the plasma membrane as well as progesterone signaling through ERK and PI3K in a mammary tumor cell line (Pedram et al., 2012).

In conclusion, the classical PR either translocate to the nucleus and alter gene transcription, or they move to the cytoplasm or plasma membrane, where they interact with components of intracellular signaling pathways, in particular with kinases. The extra-nuclear signaling of PR and other steroid receptors may play a particularly important role in neural cells. However, how PR located in axons, dendrites or at the level of synapses may influence the activity and excitability of neurons remains to be explored. Likewise, PR may regulate the functions of glial cells by interacting with other proteins within cell extensions. The time has come to explore new mechanisms of steroid receptor signaling in neurons and glial cells, and we should no longer limit ourselves to the extrapolation of observations made in cells of reproductive organs to the nervous system.

6. Brain progesterone receptors

Both PR-A and PR-B isoforms are widely expressed in the rat and mouse brain, where they show different expression patterns and regulation (Beyer et al., 2002; Guerra-Araiza et al., 2001; Kato et al., 1993). However, their respective functions in the nervous system and their respective roles in mediating the trophic and protective effects of progesterone remain to be explored; obviously a rewarding field for future investigations. A recent study has shown that the two PR isoforms differentially regulate the expression of enzymes involved in neurotransmitter metabolism within the female rat hypothalamus, namely, tryptophan hydroxylase, tyrosine hydroxylase and glutamic acid decarboxylase

(GAD). This was shown by the intracerebroventricular injection of PR-B and total PR (PR-A + PR-B) antisense oligonucleotides (Gonzalez-Flores et al., 2011).

Although the PR are widely distributed throughout the brain, they are not inducible by estrogens in all regions. The quantitative mapping of [^{3}H]promegestone in microdissected brain nuclei and regions revealed that estrogen treatment of ovariectomized female rats increased levels of PR in regions of the hypothalamus which also contain elevated levels of ER, in particular ventromedial nuclei of the hypothalamus (VMN), arcuate nucleus, median eminence, periventricular anterior hypothalamus and suprachiasmatic nuclei (MacLusky and McEwen, 1978, 1980; Parsons et al., 1982). Western blot analysis of PR isoform content in the hypothalamus has revealed that both PR-A and PR-B proteins are increased by estradiol treatment, and that their expression changes during the estrous cycle (Guerra-Araiza et al., 2003). Moderate levels of PR were induced in other hypothalamic and limbic structures, including bed nucleus of the stria terminalis, cingulate cortex, medial amygdaloid nucleus, and the CA1 subfield of the hippocampus. In contrast, PR were not found to be induced by estradiol in cerebral cortex, septum, caudate putamen, supraoptic nucleus, dentate gyrus, the CA3 subfield of the hippocampus, midbrain, and cerebellum (Camacho-Arroyo et al., 1994; MacLusky and McEwen, 1978, 1980; Parsons et al., 1982). Similarly, in the rat spinal cord and in peripheral nerves, PR expression may also not be affected by estrogen treatment (Jung-Testas et al., 1996; Labombarda et al., 2003).

Whereas estrogen-inducible brain PR are down-regulated by exposure to progesterone, PR which are not regulated by estrogen seem to be constitutively expressed, and their expression is unaltered even during prolonged progesterone treatment. Thus, expression of the PR isoforms remained unchanged by progesterone treatment in the rat frontal cortex, cerebellum and spinal cord (Camacho-Arroyo et al., 1994, 1998; Guerra-Araiza et al., 2002, 2003; Labombarda et al., 2003). This is a particularly important observation, as the promotion of neuroprotection and myelin repair may require prolonged treatment with progesterone.

As already pointed out in the previous section, we still know very little concerning the signaling mechanisms of PR in neural cells. It is indeed too easy to extrapolate from what we know of mammary and uterine PR to the brain. For example, we are only just beginning to appreciate the complexity of the interactions of steroid receptors with nuclear coactivators and corepressors in different types of neural cells. The most studied steroid receptor coactivators of the p160 family (SRC-1, SRC-2, SRC-3) are widely distributed throughout the brain and are present in hypothalamic nuclei, cerebral cortex, hippocampus, midbrain, cerebellum and brain stem (Bian et al., 2011; Meijer et al., 2000; Nishihara et al., 2003; Ogawa et al., 2001; Tetel et al., 2007; Tognoni et al., 2011; Yousefi et al., 2005; Zhang et al., 2011). At the cellular level, these coactivators are not only present within the nuclear compartment, but also in cytoplasm, as well as at the level of cell membranes and in neurites (Bian et al., 2011; Zhang et al., 2011).

In the brain, nuclear coregulators play an important role in steroid receptor-dependent gene expression, neural plasticity, development and behavior (Nishihara et al., 2004; Tetel et al., 2009). For example, inhibition of SRC-1 by the intracerebroventricular infusion of antisense oligonucleotides blocks steroid receptor-dependent gene expression within the preoptic area and inhibits the activation of male sexual behavior (Charlier and Balthazart, 2005). Importantly, the assembly of steroid receptor-coactivator complexes and their transcriptional activities differ between neural cells (Fonte et al., 2005; Grenier et al., 2006). Moreover, their expression is regulated by hormonal and environmental factors and shows age-related changes (Bousios et al., 2001; Camacho-Arroyo et al., 2005; Charlier et al., 2006; Zhang et al., 2011). These are significant findings, as coactivators are limiting factors for the transcriptional efficiency of steroid receptors, including the PR, as has been demonstrated in reproductive tissues. Thus, SRC-1 and SRC-2 have been shown to be important for the stimulation of gene expression by PR in uterus, whereas SRC-3 is the primary coactivator for PR transcriptional activity in breast (Han et al., 2006; Jeong et al., 2007). Furthermore, it is becoming evident that steroid receptor coregulators are also involved in a variety of diseases of the nervous system, including neurodegenerative disorders, and in responses to injury (Neri, 2001; Tan et al., 2009; Thakur and Paramanik, 2009). However, their potential role in modulating trophic and protective actions of PR remains to be explored.

Studying brain PR signaling during myelination and its significance for neuroprotection is particularly demanding because of their extra-nuclear localization in neurons outside the hypothalamus. Although a fraction of the extra-hypothalamic PR are translocated to the cell nucleus where they may regulate gene expression, as has been demonstrated by nuclear exchange assays within microdissected brain regions, including septum, midbrain and cerebral cortex (Blaustein and Feder, 1980; Rainbow et al., 1982a), a significant number of PR are located in neurites and at the level of synapses (Waters et al., 2008). For these extra-nuclear receptors, rapid signaling mechanisms involving cell membrane and cytoplasmic kinase pathways may play a particularly important role. However, during late fetal and early postnatal development, elevated levels of nuclear PR are transiently expressed throughout the rodent brain (see Section 12 below).

7. Mechanisms of allopregnanolone signaling: recent advances

Important milestones in the study of the psychopharmacological actions of progesterone were the discovery of the positive allosteric modulation of $GABA_A$ receptors by allopregnanolone, the characterization of the neuron-type-specific subunit composition of steroid-sensitive $GABA_A$ receptors and the identification of two sites on the $GABA_A$ receptor complex to which 3α,5α-reduced metabolites of both progesterone and deoxycorticosterone bind (Belelli et al., 2002; Hosie et al., 2006; Lambert et al., 2003; Majewska et al., 1986). The presence of specific binding sites for allopregnanolone on $GABA_A$ receptors were already predicted by the enantioselectivity of its modulatory actions (Wittmer et al., 1996; Zorumski et al., 1998). Experiments combining electrophysiological recordings and imaging of a fluorescent steroid analog have revealed that allopregnanolone does not access $GABA_A$ receptors via the aqueous extracellular space. Instead, the lipophilic steroid reaches its binding sites on the transmembrane domains via lateral membrane diffusion. Moreover, allopregnanolone can be provided by intracellular reservoirs (Akk et al., 2005). As a consequence, when designing steroid compounds for the modulation of $GABA_A$ receptors, in addition to their receptor affinity, both lipid solubility and partitioning into the plasma membrane have to be taken into account (Akk et al., 2009). Mechanisms involved in the modulation of $GABA_A$ receptors by allopregnanolone are thus distinct from the conventional access of ligands to extracellular binding domains of membrane receptors.

Other seminal studies published over the past few years have contributed to a completely new understanding of how the potentiation of $GABA_A$ receptors by allopregnanolone affects neuronal excitability. At the basis of this conceptual evolution was the observation of a particular form of $GABA_A$ receptor-mediated inhibition, termed "tonic inhibition". Whereas synaptic $GABA_A$ receptors mediate rapid phasic inhibition of postsynaptic currents, tonic $GABA_A$ receptor-mediated inhibition results from the activation of extrasynaptic receptors, which generate persistent inhibition of neuronal excitability (Farrant and Nusser, 2005;

Semyanov et al., 2004). Extrasynaptic $GABA_A$ receptors differ from their synaptic counterparts by their subunit composition and pharmacological and functional properties (Belelli and Lambert, 2005; Belelli et al., 2009). Thus, the γ2 subunit contributes to the postsynaptic localization of $GABA_A$ receptors by mechanisms involving the palmitoylation of cysteine residues, whereas δ subunit containing receptors are predominantly extrasynaptic (Alldred et al., 2005; Luscher et al., 2011). Importantly, extrasynaptic receptors containing the δ subunit are insensitive to a variety of benzodiazepines, but are sensitive targets for allopregnanolone (Farrant and Nusser, 2005; Nusser and Mody, 2002). Accordingly, δ subunit knockout mice show reduced sensitivity to neuroactive steroids (Mihalek et al., 1999; Stell et al., 2003). However, one should always be cautious with generalizations, as there are differences between distinct parts of the brain, and as the properties of $GABA_A$ receptors are influenced by many factors, including post-translational modifications such as phosphorylation (Herd et al., 2007). Thus, in thalamocortical neurons, extrasynaptic $GABA_A$ receptors were found to be relatively insensitive to neurosteroids (Belelli et al., 2009).

The expression of $GABA_A$ receptors undergoes dynamic modulations, and particularly important for our purpose are studies showing that the expression and composition of synaptic and extrasynaptic $GABA_A$ receptors is under the strong influence of the endocrine environment. This complex and rapidly evolving field has been extensively reviewed, and we shall only provide a few important examples here (Follesa et al., 2004; Glykys and Mody, 2007; Smith et al., 2007; Belelli et al., 2009). Steroid hormones have indeed been shown to alter $GABA_A$ receptor subunit expression. Thus, the expression of $GABA_A$ receptor subunits changes over the estrous cycle, and increased expression both δ and γ2 subunits are associated with increased levels of progesterone. During the high-progesterone phase of the estrous cycle (late diestrus), enhanced expression of the δ subunit in neurons of the mouse hippocampus is associated with increased tonic inhibition, reduced neuronal excitability and diminished seizure susceptibility and anxiety (Maguire et al., 2005). Interestingly, the cyclic changes in $GABA_A$ receptor subunits observed in female mice can be mimicked by treatments with progesterone in males or in ovariectomized females. The effect of progesterone is rapid and cannot be blocked by the PR antagonist mifepristone (Maguire and Mody, 2007). In contrast, the important rises in progesterone and allopregnanolone levels during pregnancy are associated with a down-regulation of both δ and γ2 subunits within the mouse hippocampus, resulting in a significant decrease in tonic and phasic inhibitions (Maguire and Mody, 2008). The decrease in δ subunit expression during pregnancy is brain region-specific, as it is observed in hippocampus, thalamus and striatum, but not in cerebral cortex (Maguire et al., 2009).

Another subunit which undergoes marked changes in expression in response to changing steroid hormone levels is the α4 subunit, which is coexpressed with either δ or γ2 subunits and is insensitive to benzodiazepines (Smith et al., 2007). Whereas α4β2γ2 $GABA_A$ receptors are localized at the synapse and extrasynaptically, α4β2δ $GABA_A$ receptors are exclusively extrasynaptic (Wei et al., 2003). Both chronic exposure to progesterone or allopregnanolone or withdrawal from these steroids increase α4 subunit expression, resulting in decreased benzodiazepine sensitivity and neuronal hyperexcitability. Natural states of steroid withdrawal associated with increased α4 subunit expression are encountered during the estrous cycle and at parturition, and they have been related to premenstrual and post-partum symptoms: increased anxiety, seizure susceptibility, depression and insensitivity to benzodiazepine sedatives (Smith et al., 1998a,b).

As allopregnanolone activates both synaptic and extra-synaptic $GABA_A$ receptors, variations in its brain levels can be expected to produce important changes in neuronal excitability. Variations in the local concentrations of allopregnanolone may result either from changes in its metabolism or synthesis, and their consequences for $GABA_A$ receptor activity have been investigated by electrophysiological techniques. Thus, the local metabolism of allopregnanolone contributes to the low sensitivity of GABAergic synapses to the neurosteroid within the dentate gyrus. In contrast, within another subregion of the hippocampus, named CA1, neurons respond to low concentrations of allopregnanolone, as its metabolism is less active (Belelli and Herd, 2003). Another study has demonstrated that the spatially restricted synthesis of allopregnanolone determines differences in synaptic $GABA_A$ receptor activity, which is observed between different layers of neurons in the rat spinal dorsal horns during postnatal development (Inquimbert et al., 2008).

Signaling mechanisms of allopregnanolone may not be limited to $GABA_A$ receptors, as additional targets of the neurosteroid have been recently identified. The pregnane X receptor (PXR) has been proposed to mediate part of the neuroprotective effects of allopregnanolone in a mouse model of Niemann-Pick type C disease (Langmade et al., 2006). This receptor, which was discovered 15 years ago, acts as a ligand-activated transcription factor. It senses many structurally unrelated compounds, ranging from steroids to clinical drugs, and regulates the expression of genes involved in xenobiotic detoxification and apoptosis (Kortagere et al., 2012; Orans et al., 2005). Its biological significance for neuroprotective actions of allopregnanolone thus remains to be clarified.

At the level of the plasma membrane, both progesterone and allopregnanolone also bind to membrane progesterone receptors (mPR), which are unrelated to the classical intracellular PR. Hydrophilicity and transmembrane analysis predicted proteins with seven transmembrane domains. They may be directly coupled to G proteins, activate pertussis-sensitive inhibitory G proteins and down-regulate adenylyl cyclase activity (Thomas, 2008; Zhu et al., 2003). Allopregnanonolone acts as a potent mPR agonist on the immortalized hypothalamic neuronal cell line GT1-7, which secretes luteinizing hormone-releasing hormone (LHRH) in a pulsatile manner. At low nanomolar concentrations, allopregnanolone mimicked the actions of progesterone: decreased cAMP accumulation and anti-apoptotic effects (Thomas and Pang, 2012). The mPR could mediate neuroprotective actions of allopregnanolone and progesterone throughout the central nervous system (CNS), as they are widely and abundantly distributed in the brain and spinal cord of both male and female rats and mice (Labombarda et al., 2010; Meffre et al., 2013). Within the mouse spinal cord, mPR are expressed in most neurons, astrocytes, oligodendrocytes, and also in a large proportion of oligodendrocyte progenitor cells (OPC), suggesting pleiotropic actions (Labombarda et al., 2010). In contrast, mPR is only present in neurons of the intact brain, but the receptor is induced in astrocytes, oligodendrocytes and microglial cells in response to TBI, pointing to a possible role of mPR in the neuroprotective, immunomodulatory and promyelinating effects of allopregnanolone and progesterone (Meffre et al., 2013).

8. Levels of progesterone and allopregnanolone in women and female rodents

Before discussing changes in progesterone and allopregnanolone levels in response to stress and injury of the nervous system, for appreciating the presence of progesterone in males and its synthesis within the nervous system, it is useful to provide physiological reference values. The most important physiological changes in circulating progesterone are observed in females during their cycle and during pregnancy. Progesterone is indeed

best-known for its role in pregnancy. Produced by the corpus luteum of the ovary, progesterone prepares the uterus for implantation, and ovarian progesterone supports pregnancy during the first weeks post-conception (Chabbert-Buffet et al., 1998). In humans, progesterone synthesis is taken over by the syncytiotrophoblasts of the placenta after about 6–8 weeks of pregnancy (Miller, 1998; Tuckey, 2005). As the placenta is part of the fetus, mutations disrupting the progesterone biosynthetic pathway are obviously not compatible with the continuation of pregnancy. There is however one report of a child born prematurely in spite of a severe disruption of the P450scc enzyme due to a mutation of the *CYP11A1* gene. If confirmed, this observation suggests that deficiency of placental progesterone synthesis may be compatible with fetal survival under particular circumstances (Hiort et al., 2005). In contrast to humans, the maternal corpus luteum remains functional and produces progesterone throughout gestation in rodent species. This explains why mice knockout for the *CYP11A1* gene develop until birth, and only die afterwards because of steroid deficiency (Hsu et al., 2006).

Very high levels of progesterone are reached in the course of human pregnancy, culminating at 10^{-7} M concentrations during the third trimester (200–400 nM) (Fig. 2). At the same time, 5α-DHP and allopregnanolone levels respectively peak around 100 nM and 30 nM, as shown by gas chromatography/mass spectrometry (GC/MS) (Gilbert Evans et al., 2005; Hertig et al., 2010; Parizek et al., 2005). Analysis of the steroid metabolome by GC/MS within maternal and fetal compartments at specific stages of gestation and during pathological changes has revealed the complexity of hormonal changes during pregnancy (Hertig et al., 2010; Hertig and Liere, 2010; Hill et al., 2007, 2010).

When compared to pregnancy, circulating levels of progesterone are low in women during the follicular phase of the menstrual cycle (1–3 nM), and they transiently and markedly rise during the luteal phase (20–40 nM) (Genazzani et al., 1998; Havlikova et al., 2006; Mumford et al., 2010). Basal levels of progesterone similar to those observed during the follicular phase are also present in postmenopausal women (Genazzani et al., 1998) (Fig. 2). It is important to note that the production of progesterone by the ovaries not only shows cyclic changes, but that the hormone is secreted in a pulsatile manner and in a luteinizing homone (LH)-dependent fashion (Ellinwood et al., 1984; Filicori et al., 1984). In women, circulating progesterone indeed rapidly fluctuates from levels as low as 6 nM to peaks of 120 nM within the course of minutes, correlating with LH pulsatile release during the mid-late luteal phase (Filicori et al., 1984; Veldhuis et al., 1988). However, not all pulses of progesterone are accompanied by LH pulses, suggesting some degree of autonomy of the corpus luteum, which has its own progesterone pulse generator (Bah et al., 2006; Rossmanith et al., 1990; Wuttke et al., 1998). Pulses of ovarian progesterone and estradiol frequently occur simultaneously. The rapid pulsatility of progesterone secretion may gain all its significance in the light of the rapid cycling of PR on chromatin discussed above, which may be important for functional outcomes.

Coupling of ChIP-seq with microarray analysis has revealed that progesterone also regulates the expression of clock genes involved in circadian rhythms within the mouse uterus (Rubel et al., 2012). The use of knockout mice demonstrated that progesterone regulation of clock gene expression requires the PR. Thus, progesterone signaling via PR may be involved in the regulation of daily oscillations within progesterone target tissues. It is indeed now well established that in addition to the master clock in the suprachiasmatic nucleus of the hypothalamus, virtually all cells express clock genes and possess their internal circadian clocks, which may have a major influence on hormone signaling (Kennaway et al., 2012; Teboul et al., 2008).

Whereas progesterone is secreted by the ovaries during the menstrual cycle in a cyclic manner, the hormone is produced in a continuous manner throughout pregnancy because constantly elevated levels of progesterone are needed for the maintenance of pregnancy. This explains why the regulation of progesterone

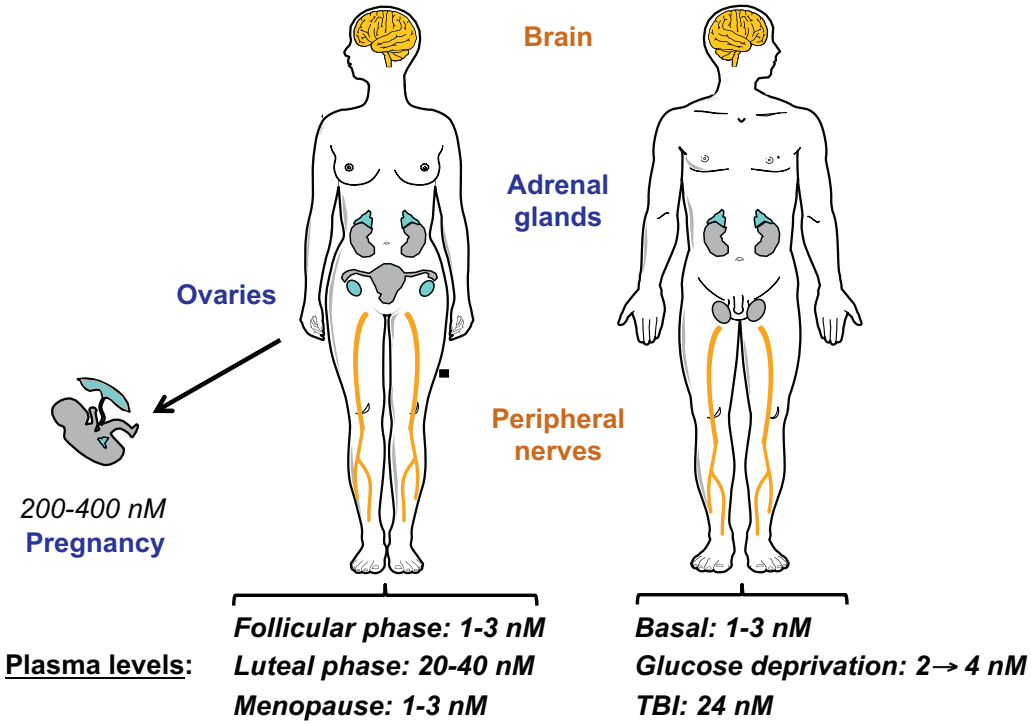

Fig. 2. Sources of progesterone (in blue for the endocrine glands and in yellow for the nervous system) and its plasma reference levels in women and men. Ranges of concentrations encompass those reported in the studies quoted in the present review. Depending on the studies, levels of progesterone reported for the central and peripheral nervous systems are either in equilibrium with plasma levels or significantly higher. TBI: plasma level after traumatic brain injury.

synthesis in placenta fundamentally differs from that in the other steroidogenic endocrine glands (Tuckey, 2005). However, progesterone secretion has been reported displaying a diurnal rhythm in pseudopregnant rats (Bischof et al., 1973).

In rodent species used for experimental studies, the reproductive cycle is named the "estrous cycle". Its features have been mainly studied in rats, as they can be easily manipulated (Westwood, 2008). Female rats have rapid cycles of 4–5 days, but most studies report hormonal changes for 4-day cyclers, and the different days of the cycle are commonly named proestrus, estrus, diestrus-1 and diestrus-2 (diestrus-1 and diestrus-2 are also frequently referred to as metestrus and diestrus, respectively). Estrogen levels peak during proestrus, followed by the LH surge which triggers ovulation and formation of the corpus luteum (McCracken et al., 1999). Concerning changes in hormone levels during the cycle, individual studies should always be interpreted cautiously because of marked differences between strains, environmental influences, and also because different assay and sampling procedures have been used (Haim et al., 2003). Nevertheless, a general picture can be derived from a series of studies, with progesterone levels being low during estrous and at the end of diestrus-2 (10–20 nM) and reaching twice peak values: during proestrus, that is prior to sexual receptivity, and during diestrus-1 (60–120 nM, concentration ranges encompassing those reported in the quoted studies) (Baranda-Avila et al., 2009; Butcher et al., 1974; Haim et al., 2003; Kalra and Kalra, 1974; Smith et al., 1975). Importantly, the cyclic changes in circulating progesterone are reflected by variations in brain levels of progesterone, 5α-DHP and allopregnanolone (Kellogg and Frye, 1999). During gestation, circulating levels have been reported to reach about 250 nM for progesterone and 30 nM for allopregnanolone, and similar levels of both hormones have been measured in cerebral cortex, consistent with the fact that they easily cross the blood brain-barrier and rapidly diffuse throughout nervous tissues (Concas et al., 1998). This increase in progesterone and allopregnanolone during pregnancy drives important changes in the mother's brain (Brunton and Russell, 2008).

Studies of hormonal changes during the estrus cycle are more difficult to perform in mice, as they are not so easy to handle as rats, and as they are very sensitive to the disrupting effects of stress. Nevertheless, the increasing use of transgenic mouse lines requires characterization of their reproductive biology (Caligioni, 2009). Reported peak values of progesterone levels during the mouse estrous cycle are about 60 nM, similar to those measured in female rats, with a tendency for persisting higher levels during diestrus-2 (Bastida et al., 2002; DeLeon et al., 1990; Walmer et al., 1992; Wood et al., 2007). During gestation, by the end of the third week, plasma levels of progesterone reaching 150–300 nM have been reported (Barkley et al., 1979; Murr et al., 1974; Piekorz et al., 2005; Virgo and Bellward, 1974).

We may thus provide the following schematic summary for changes in circulating progesterone levels in females: they reach the 10^{-7} M range during pregnancy and the 10^{-8} M range during peaks of the reproductive cycles. In contrast, basal concentrations of progesterone, most likely of adrenal origin, are in the low nanomolar range. They are observed during the follicular phase and during menopause in women (Fig. 2). Interestingly, increases in progesterone appear to be accompanied by increases in its 5α-reduced metabolites. Moreover, studies in rodents suggest an equilibrium between plasma and brain levels of progesterone (Concas et al., 1998; Kellogg and Frye, 1999; Meffre et al., 2007).

9. Facilitation of female rodent sexual behavior by progesterone and allopregnanolone

As already pointed out, studies of brain PR have mainly focused on their regulation within the hypothalamus and their significance in the activation of female reproductive behaviors. A large number of experimental studies have examined the role of progesterone in relation to the regulation of sexual behavior in female rodents, precisely their role in the activation of lordosis, a posture females take in response to mounts by a male (Pfaff et al., 2008). This stereotyped and strictly hormone-dependent behavioral response represents a unique model in which to study steroid actions on neural cells. Already in 1936, it was shown that the sequential action of estradiol and progesterone is required to induce sexual receptivity in ovariectomized guinea pigs (Dempsey et al., 1936), and this was subsequently confirmed in rats and mice (Boling and Blandau, 1939; Ring, 1944). This was only two years after the advent of crystalline progesterone (Butenandt and Westphal, 1934; Hartman and Wettstein, 1934; Slotta et al., 1934; Wintersteiner and Allen, 1934).

Since then, the study of lordosis behavior has allowed remarkable progress in our understanding of the effects of estradiol and progesterone on the brain and on behavior. The rise in circulating estradiol between diestrus and proestrus, or the treatment of ovariectomized female rats with estrogen, were shown to induce PR in hypothalamic neurons (McGinnis et al., 1981a; Moguilewsky and Raynaud, 1979a; Romano et al., 1989; Scott et al., 2002). Double-label immunocytochemistry revealed that virtually all PR-positive hypothalamic neurons contain ER-immunoreactivity (Blaustein and Turcotte, 1989; Warembourg et al., 1989). The induction of hypothalamic PR by estrogen was then shown to be required for the facilitation of the lordosis response by progesterone. Indeed, nuclear translocation of hypothalamic PR precedes the appearance of lordosis behavior, and the time course of the induction of hypothalamic PR by estradiol parallels the time course of the induction of behavioral sensitivity to progesterone (Blaustein and Feder, 1979; McGinnis et al., 1981b; Parsons et al., 1980, 1981b; McEwen et al., 1982). Moreover, infusion of PR antisense DNA into the hypothalamus of estrogen-primed female rats inhibited the facilitation of lordosis behavior by progesterone (Mani et al., 1994; Ogawa et al., 1994). The VMN are the main hypothalamic nuclei where the concerted actions of estradiol and progesterone facilitate the lordosis response (Barfield et al., 1984; McEwen et al., 1979; Schumacher et al., 1990).

Studies in knockout mice with selective PR-A or PR-B ablation have established a critical role for the PR-A isoform in the facilitation of reproductive behavior in female mice by progesterone. However, although the PR-A isoform appears to be necessary, the lordosis response was reduced in the absence of PR-B (Mani et al., 2006). In another study, the intracerebroventricular injection of PR-B antisense oligonucleotides efficiently inhibited lordosis behavior induced by progesterone, but total PR (PR-A + PR-B) antisense oligonucleotides were more efficient (Guerra-Araiza et al., 2009). Taken together, these observations suggest a major contribution of both PR isoforms to the faciliation of female sexual behavior. Many studies have been devoted to the mechanisms by which hypothalamic PR facilitate lordosis behavior. They have shown that the modulation of multiple signal transduction mechanisms are involved, and they point to a key role of cross-talk between PR and neurotransmitter and growth factor signaling pathways (Etgen et al., 2006; Gonzalez-Flores et al., 2004; Mani and Portillo, 2010).

Importantly, it is also possible to facilitate the lordosis response in females by treatment with allopregnanolone. This was first shown in female hamsters and later confirmed in female rats (Debold and Frye, 1994; Frye et al., 1998). A possible explanation could have been the conversion of the administered allopregnanolone to 5α-DHP, which in turn activates PR as discussed above (Rupprecht et al., 1993). Consistent with such an explanation was the observation that the effect of allopregnanolone could be

inhibited by the PR antagonist mifepristone (Beyer et al., 1995; Gonzalez-Mariscal et al., 1989). However, it was then shown that allopregnanolone treatment can also activate lordosis behavior in PR knockout mice, pointing to a PR-independent signaling pathway of allopregnanolone involved in the facilitation of female reproductive behavior (Frye et al., 2006b). This pathway has been identified: allopregnanolone facilitates lordosis behavior, as well as other socio-sexual and motivated behaviors, by modulating $GABA_A$ receptor activity located within the midbrain ventral tegmental area (VTA) (Frye et al., 2008; Frye, 2011). The modulation of $GABA_A$ receptors in the VTA by allopregnanolone appears to be a physiological regulatory process of behavior, as endogenous levels of allopregnanolone are significantly increased in this brain region during mating (Frye et al., 2007). Moreover, inhibition of brain allopregnanolone formation reduces the lordosis response (Frye et al., 2008; Petralia et al., 2005).

However, subcutaneous injections or intravenous infusion of high doses of progesterone do not facilitate lordosis behavior in estrogen-primed PR knockout female mice (Frye et al., 2006b; Lydon et al., 1995). These observations provided substantial proof that PR play an essential role in the activation of female reproductive behavior, and they also showed that the endogenous conversion of progesterone to allopregnanolone is not sufficient to activate the behavior in the absence of the PR (otherwise, the administration of exogenous progesterone would also have facilitated lordosis behavior in PR knockout mice via its conversion to allopregnanolone). These results have to be kept in mind when discussing later the neuroprotective effects of progesterone and allopregnanolone (see Section 16).

In summary, the use of a pharmacological antagonist, antisense DNA and knockout mice has clearly established a key role of hypothalamic PR in the activation of female sexual behavior by progesterone in rodents. Moreover, both PR-A and PR-B isoforms seem to be essential for optimal behavioral responses. However, even in the absence of PR, it is possible to facilitate lordosis responses by the administration of exogenous allopregnanolone, which activates a PR-independent pathway involving midbrain $GABA_A$ receptors.

10. Progesterone and allopregnanolone in males

It would be a misconception to consider progesterone solely as a female reproductive hormone. In both men and women, significant amounts of progesterone are produced by the adrenal glands under the control of adrenocorticotropic hormone (ACTH). In women, progesterone is produced by the adrenal cortex during the follicular phase, whereas the ovaries become the main source of the hormone prior to ovulation (De Geyter et al., 2002; Genazzani et al., 1998). Thus, during the follicular phase, secretion of progesterone can be stimulated by ACTH, whereas during the luteal phase, levels of progesterone increase in response to luteinizing hormone (LH).

In men, progesterone in the circulation is of adrenal origin (Gutai et al., 1977). For young healthy men, low concentrations of progesterone have been reported (1–3 nM) (Fig. 2). However, in response to a variety of stressors, such as inflammation and glucose deprivation, levels of progesterone almost double (Elman and Breier, 1997; Zitzmann et al., 2005). A recent study has reported a striking increase in circulating progesterone in men after TBI, reaching levels of about 24 nM, intermediate between those measured for women during their follicular and luteal phase. However, this increase in progesterone is transient, and its levels returned to control values (about 2–3 nM) within 24–48 h (Wagner et al., 2011). Levels of cortisol were also significantly increased in response to TBI, but in contrast to those of progesterone, they remained elevated for several days. It is important to note that adrenal responses are blunted in patients with severe TBI and after the use of adrenal suppressing agents (Cohan et al., 2005; Llompart-Pou et al., 2007).

Basal levels of progesterone do not decrease with age in men, and are comparable to those measured in women during their follicular phase and menopause (Belanger et al., 1994; Genazzani et al., 1998; Oettel and Mukhopadhyay, 2004; Vermeulen and Verdonck, 1976). In addition, PR are largely distributed in various tissues in men, including hypothalamus, pituitary gland, mammary gland and parts of the male genital tract (Luetjens et al., 2006). Indirect evidence for functional PR in the brain of men has been provided by clinical trials aimed at testing methods of hormonal contraception. They have indeed shown that combining testosterone with a progestin is more efficient in suppressing spermatogenesis than testosterone given alone. The facts that progestins inhibit gonadotropin secretion, and that the PR-selective 19-norpregnane derivative Nestorone provides efficient contraception when administered together with testosterone, suggest a role of PR at the level of the hypothalamus and pituitary glands (Ilani et al., 2012; Mahabadi et al., 2009; Page et al., 2008).

Both synthesis and secretion of adrenal progesterone can also be stimulated by ACTH in laboratory rodents, and progesterone is present in the circulation of males at significant levels (Feder and Ruf, 1969; Kalra and Kalra, 1977; Resko, 1969). Moreover, the hypothalamus of both male and female rats contains significant amounts of PR, and whether the subtle differences between sexes in the number of hypothalamic receptors accounts for differences in neuroendocrine and behavioral responses remains uncertain (Blaustein et al., 1980; Bogic et al., 1988; Rainbow et al., 1982b).

Consistent with an adrenal origin of progesterone, male rats continue to exhibit stress-induced progesterone secretion after removal of their testes (Schaeffer and Aron, 1987). Interestingly, progesterone secretion by the adrenal glands in response to restraint stress is much stronger in pre-pubertal male rats when compared to adults, and puberty is characterized by marked changes in adrenocortical responsiveness to stress (Romeo et al., 2005; Romeo, 2010). In male mice, circulating progesterone analyzed by GC/MS was found to be strongly upregulated in response to surgical stress, and to reach levels comparable to the ones observed during proestrus in females (up to 20 nM) (Liu et al., 2012).

In addition to the adrenal glands, progesterone is also synthesized within the male brain and spinal cord, where it qualifies as a neurosteroid. The synthesis of progesterone has indeed been demonstrated in the nervous system of all species studied so far, and the enzymes required for progesterone and allopregnanolone synthesis are widely distributed throughout the brain (Do Rego et al., 2009; Guennoun et al., 1995; Ibanez et al., 2003; Mellon and Griffin, 2002; Mensah-Nyagan et al., 1999; Tsutsui, 2008). In multiple regions throughout the rodent brain, 5α-reductase and 3α-HSD were shown to co-localize in the same glutamatergic and GABAergic neurons, suggesting synthesis and the modulation of neurotransmission by allopregnanolone (Agis-Balboa et al., 2006). Importantly, levels of progesterone were found to be strongly upregulated in the CNS of male rats in response to injury, even after removal of their steroidogenic endocrine glands, strongly suggesting increased synthesis (Labombarda et al., 2006). Levels of brain progesterone are also upregulated after TBI in rats and after ischemic brain injury in mice (Liu et al., 2012; Meffre et al., 2007).

There is evidence that neurosteroids, and in particular progesterone, may also be synthesized within the human brain (Schumacher et al., 2003; Stoffel-Wagner, 2001). The presence of the cytochrome P450scc was first detected in the human brain by immunocytochemistry (Le Goascogne et al., 1989), and several studies have described the presence of P450scc mRNA in different

brain regions (Beyenburg et al., 1999; Inoue et al., 2002; King et al., 2002; Watzka et al., 1999; Yu et al., 2002). The type 2 isoform of the human 3β-HSD is also largely expressed in the human brain, as are the enzymes necessary for the metabolism of progesterone to 5α-DHP and allopregnanolone (the 5α-reductase-3α-HSD complex) (Inoue et al., 2002; Steckelbroeck et al., 2001; Stoffel-Wagner et al., 2003; Yu et al., 2002).

Unfortunately, the physiological functions of progesterone remain largely unexplored in males. It has been proposed that in men, progesterone may play a significant role in general health (Muneyyirci-Delale et al., 1999; Oettel and Mukhopadhyay, 2004). Because of the important production of progesterone by the adrenal glands in response to stressful stimuli and its dependence on ACTH stimulation, progesterone may qualify as a "stress hormone". In both sexes, progesterone may be an important modulator of adaptative responses to stress and of anxiety, and these effects may be mainly mediated by allopregnanolone and the potentiation of $GABA_A$ receptor responses, as discussed in the next section. Progesterone and allopregnanolone have indeed been shown to modulate stress responsiveness in both males and females (Patchev et al., 1994; Patchev and Almeida, 1996). Moreover, in both men and women, progesterone therapy has been found to dampen psychological responses to stress (Childs et al., 2010; Del et al., 1998). In addition, progesterone and allopregnanolone, and in particular their synthesis within the nervous system, may play an important role in neuroprotective and neuroregenerative mechanims in both males and females, as discussed in sections 15 and 16.

11. Modulation of stress responsiveness and anxiety-like behavior by progesterone and allopregnanolone

The endocrine stress response system is the hypothalamo–pituitary–adrenal (HPA) axis. Its activation by stressful stimuli involves the stimulation of hypothalamic corticotropin-releasing hormone (CRH) neurons and the release of ACTH by the anterior pituitary gland, which stimulates the secretion by the adrenal glands of glucocorticoids and of progesterone. Glucocorticoids in turn regulate responses of the entire body to stress and exert marked effects on brain functions and neural functions and plasticity (Brunton and Russell, 2011; McEwen, 2010; Popoli et al., 2012).

Progesterone and allopregnanolone, in addition to the glucocorticoids, exert major influences on stress responses in both sexes. Both hormones have been shown to be upregulated in plasma and cerebral cortex of male rats in response to swim stress, and this stress response was inhibited by adrenalectomy (Purdy et al., 1991). A series of studies have demonstrated that the anti-stress effects of progesterone and allopregnanolone, as those of 3α,5α-tetrahydrodeoxycorticosterone, involve modulation of brain $GABA_A$ receptor neurotransmission (Barbaccia et al., 2001). In addition, both progesterone and allopregnanolone have been shown to modulate, in a specific manner, the expression of stress-responsive genes in the brain of adult male and female rats (Patchev et al., 1994; Patchev and Almeida, 1996). The mechanisms through which allopregnanolone exerts its transcriptional effects are still not completely understood, and may involve the transcriptional activation of PR after its conversion back to 5α-DHP (Rupprecht et al., 1993). Alternatively, allopregnanolone may regulate gene expression via the modulation of $GABA_A$ receptors. Indeed, $GABA_A$ receptor activity can influence gene transcription via the activation of downstream signal transduction pathways (Auger et al., 2001; Berninger et al., 1995; Delgado and Owens, 2012; Brinton, 2013).

Stress can lead to an imbalance of the neural circuitry of anxiety, comprising the prefrontal cortex and amygdala (Damsa et al., 2009; McEwen et al., 2012). Anxiety is an adaptative reaction to potential threats, characterized by increased arousal, autonomic and neuroendocrine changes (Steimer, 2002). However, anxiety can become a pathological state, and different types of anxiety disorders have been described, including generalized anxiety, panic, post-traumatic stress, obsessive-compulsive and phobia disorders (Martin et al., 2010). Many experimental models of anxiety and anxiety disorders with either unconditioned or conditioned responses have been developed in rats and mice (Haller and Alicki, 2012; Steimer, 2011).

Drugs which enhance $GABA_A$ receptor-mediated inhibition of neuronal activity, such as benzodiazepines, are effective anxiolytic substances. It is thus not surprising that allopregnanolone has marked anxiolytic effects, as demonstrated in a variety of experimental paradigms (Rupprecht, 2003). In female rats, intracerebroventricular injection of allopregnanolone has anxiolytic-like effects involving $GABA_A$ receptors (Bitran et al., 1991). Importantly, increasing brain allopregnanolone levels by the administration of progesterone or TSPO ligands, has anxiolytic-like effects in both male and female rats, which could be blocked by 5α-reductase or $GABA_A$ receptor inhibitors (Bitran et al., 1995, 2000; Brot et al., 1997; Rupprecht et al., 2010).

These results indicate a key role of $GABA_A$ receptor modulation by allopregnanolone in the anxiolytic actions of progestogens. PR seem not to be required, as progesterone and allopregnanolone also exert anxiolytic effects in PR knockout mice (Reddy et al., 2005). Interestingly, the brain remains sensitive to the anxiolytic effects of progestogens during aging. Thus, progesterone also decreased anxiety behavior in middle-aged (9–12 months) and old (18–24 months) wild-type and PR knockout mice (Frye et al., 2006a).

12. Sources of progesterone and allopregnanolone and progesterone receptors during brain development and myelination

In humans, CNS myelination begins in utero during the second trimester of gestation (see Section 14). At this time, the fetal brain is constantly exposed to high concentrations of progesterone. Circulating progesterone drops at birth and remains low until puberty, with similar levels in boys and girls (about 0.5–1 nM) (Elmlinger et al., 2002; Holmes et al., 2004; Lee et al., 1976; Lee and Migeon, 1975; Zec et al., 2012). However, during the first 2 weeks post-partum, the median concentrations of progesterone and other steroids are higher than thereafter (Elmlinger et al., 2002). Small amounts of progestins used for contraceptive purposes may reach the child via the milk of the mother. Nowadays, the only contraceptives recommended during lactation are either progesterone, which is destroyed after oral intake, or microdoses of progestins (progestin only pills) (Toddywalla et al., 1995).

In rats and mice, myelin formation in the CNS only starts after birth and is maximal between the second and third postnatal week (Bjelke and Seiger, 1989; Craig et al., 2003; Foran and Peterson, 1992). What do we know about postnatal levels of progesterone in these species? In the evening following parturition, female rats ovulate again and become sexually receptive. This postpartum estrus usually occurs during the first 24 h following parturition and circulating progesterone reaches very high levels (100–150 nM) (Carrillo-Martinez et al., 2011; Connor and Davis, 1980a,b). If a female rat fails to conceive during this period, a lactational diestrus begins without estrous cycles and continues until the pups are weaned. During this time, maternal levels of progesterone remain high (levels reported in the different studies range between 70 and 400 nM) (Berg et al., 2002; de Sousa et al., 2010; Grota and Eik-Nes, 1967; Hansen et al., 1983; Smith and Neill, 1977). However, if a female does conceive, the postpartum mating will be followed by

simultaneous gestation and lactation (Connor and Davis, 1980b). Thus, in each case, levels of circulating progesterone in the mother are elevated during the period of lactation, but the brains of the pups are not necessarily exposed to such high levels. Indeed, progesterone is metabolized in the rat mammary gland and is only present at very low levels in milk. Moreover, after its oral intake by the pups, progesterone is rapidly metabolized in the digestive system and during the first pass through the liver (Alexandrova and Macho, 1983; Massai et al., 2000). However, in contrast to natural progesterone, some synthetic progestins given to lactating females can have an influence on the pups, as has been shown for medroxyprogesterone acetate(Holzhausen et al., 1984). Developmental studies have confirmed that in rat pups of both sexes, circulating levels of progesterone are indeed low during the first 10 days of life (3–4 nM), and then progressively increased until puberty to concentrations of about 10–20 nM. Thereafter, progesterone levels drop in males to adult levels (Dohler and Wuttke, 1974, 1975). It has been proposed that circulating progesterone in prebubertal rats may originate from the adrenal glands (Dohler and Wuttke, 1975).

It has to be emphasized that circulating levels of progesterone were measured by radioimmunoassay (RIA) in these studies, and that accurate steroid profiling during development using GC/MS awaits to be performed. Moreover, plasma levels of progesterone do not tell us to which concentrations the developing neural cells are exposed. Indeed, as already mentioned, progesterone and allopregnanolone are also synthesized within the brain, where they act in an autocrine or paracrine manner and may regulate developmental processes (Mellon, 2007). The analysis of progesterone in the male rat brain by GC/MS between birth and adulthood indeed showed higher levels in hippocampus when compared to plasma, although in the low nanomolar range, with significantly higher brain levels the day of birth (Ibanez et al., 2003). Consistent with this result, analysis of the developmental expression of 3β-HSD mRNA expression in the brain showed a large distribution and neuronal expression of the enzyme; higher levels of expression being found during the first two postnatal weeks when compared to adults (Ibanez et al., 2003). Developmental expression of both P450scc and 3β-HSD mRNA in many regions of the rat brain throughout development has also been demonstrated by semi-quantitative RT-PCR (Kohchi et al., 1998). Expression of 3β-HSD by OPC and their capacity to convert progesterone to allopregnanolone at this particular developmental stage strongly suggest that progesterone synthesis and metabolism may play an important role in oligodendrocyte maturation and myelination (Gago et al., 2001).

Brain levels of allopregnanolone indeed show marked variations during development. Thus, elevated concentrations of allopregnanolone (about 50 nM) were measured in the rat forebrain at embryonic day 18. Its levels then decreased until a second rise at birth (about 8 nM) and a third rise between postnatal days 10 and 14 (about 10 nM). These changes in allopregnanolone levels were associated with modifications in brain $GABA_A$ receptor activity (Grobin and Morrow, 2001). The synthesis of allopregnanolone within the embryonic and neonatal brain may play an important role in the proliferation of neural progenitors and may also influence the wiring of neuronal circuits (Gago et al., 2004; Grobin et al., 2003).

The significance of the brain synthesis of progesterone in neuronal development has been studied in the cerebellum. In rodents, the differentiation of cerebellar neurons is a late process, which takes part during the neonatal period (Altman, 1972). During this period, Purkinje neurons synthesize progesterone and allopregnanolone (Ukena et al., 1999). Progesterone promotes the maturation of the Purkinje neurons and stimulates the formation of dendrites and synapses. The neurotrophic effects of progesterone involved PR, as its effects were not mimicked by allopregnanolone, but could be blocked by mifepristone (Sakamoto et al., 2001, 2002).

What do we know about the developmental expression of brain PR? In the developing rat brain, PR immunoreactivity can be detected as early as embryonic day 17 (E17) and is extensive between E18 and postnatal day 28 (P28) when analyzed by classical immunohistochemical procedures. During this period, nuclear PR immunoreactivity is present in the hypothalamus, limbic system, cerebral cortex, basal ganglia, thalamus as well as in the subventricular zone and choroid plexus (Quadros et al., 2007). As in the forebrain, significant levels of PR immunoreactivity are observed in numerous regions of the postnatal rat midbrain and hindbrain, including midbrain dopaminergic cell groups such as the substantia nigra and the ventral tegmental area (Quadros et al., 2008).

At E18, expression of PR in the cortical subplate, a transient zone containing precocious neurons involved in the development of cortical connections, is upregulated by maternal thyroid hormones (Jahagirdar et al., 2012; Jahagirdar and Wagner, 2010). PR expression in the developing cortex is not regulated by estradiol and is similar in males and females (Lopez and Wagner, 2009). Double-labeling immunohistochemistry indicated that PR immunoreactivity mainly colocalizes with neuronal markers (Lopez and Wagner, 2009). Within the hypothalamus, the regulation of PR expression differs between specific nuclei and is dependent on developmental stage. Thus, during the first postnatal days, PR expression is inducible by estradiol within the medial preoptic nucleus (MPN) of both male and female rat pups, but not in the VMN. As brain levels of estradiol are elevated in the neonatal male brain, resulting from the aromatization of elevated levels of testosterone to estradiol, males have much higher levels of PR immunoreactivity in the MPN than females during the first two postnatal weeks (Quadros and Wagner, 2008). Within the VMN, expression of PR becomes increasingly dependent on estradiol only after P14 (Quadros and Wagner, 2008). These findings point to an important role of PR in the developing brain. Unfortunately, we could not find information concerning the developmental expression of PR in the human brain. It is indeed difficult to study the expression of steroid receptors in postmortem brain tissue (Fodor et al., 2002).

13. Neuroprotective effects of progesterone and allopregnanolone during brain development

The developing human brain is continuously exposed to elevated levels of progesterone, 5α-DHP and allopregnanolone, which may play a key role in protection of immature neurons and in the maturation of developing neuronal circuits (Peper et al., 2011). Although the role of progesterone and other steroid hormones in brain maturation remains largely unexplored, it has been proposed that the disrupted supply of progesterone and estradiol after early preterm birth may contribute to the frequently observed impairment of neurodevelopment, with delayed psychomotor and mental development and sometimes severe neurological deficits like cerebral palsy (Trotter et al., 1999, 2012). Thus, the effects of postnatal estradiol and progesterone replacement on brain development in extremely low birth weight children have been considered. Infants with a gestational age of less than 29 weeks and a birth weight below 1000 g received intravenously a lipid emulsion containing an elevated dose of progesterone and estradiol for a maximum of 4 weeks to mimic intrauterine plasma levels of the hormones. A placebo group receiving the same emulsion without hormones was constituted. No negative side-effects attributable to the hormone treatment were observed, and infants with estradiol and progesterone replacement showed

trends toward improved bone mineral accretion and reduced incidence of chronic lung disease. However, the evaluation of cognitive and neurological outcomes at the age of 5 years revealed only slight improvements (Trotter et al., 2012). At present, there is still no well-established intervention for protecting the fetal brain, and there is an urgent need for neuroprotective treatments (Robertson et al., 2012). It is important to draw attention to the fact that preparations of natural progesterone or synthetic progestins (17-α-hydroxyprogesterone caproate) are administered to pregnant women for the prevention of preterm birth, although we still know very little concerning their impact on neonatal outcomes (Christian et al., 2007; Fontenot and Fantasia, 2012; Ness et al., 2006).

What do animal experiments teach us about potential protective and trophic effects of progesterone on the developing brain? Extensive work in sheep, a precocial species with an average 147 day gestation period, points to an important role of allopregnanolone in protecting the fetal brain. Thus, concentrations of allopregnanolone and expression of the 5α-reductase type-2 in the brain significantly rise in response to acute hypoxic stress caused by a 10 min umbilical cord occlusion at 135 days of gestation (Hirst et al., 2006). This increase in brain allopregnanolone may correspond to a neurosteroid response involved in the protection of the fetal brain against hypoxia-induced cell death. Indeed, administration of the 5α-reductase inhibitor finasteride reduced the brain allopregnanolone content and increased neural cell death (Yawno et al., 2007). This finding also suggests that the abrupt decline in allopregnanolone levels after birth may contribute to the great vulnerability of neonates to brain injury.

A dramatic protective effect of allopregnanolone during brain development has been demonstrated in a mouse model of Niemann-Pick type C (NP-C) disease. This fatal childhood neurodegenerative disease is caused by mutations in the genes encoding either NPC1 or NPC2 proteins, which are involved in the intracellular transport of cholesterol and its release from the late endosome. The NP-C mouse recapitulates cholesterol and sphingolipid storage problems, neurological deficits, Purkinje cell loss, demyelination and early death typical of the most severe form of human NP-C (Griffin et al., 2004). In brains of postnatal NP-C mice, 5α-reductase and 3α-HSD activities are markedly reduced. Remarkably, replacement therapy with allopregnanolone alleviated the neurodegenerative features of NP-C. When administered early during postnatal life, a single injection of allopregnanolone was sufficient enough to significantly delay Purkinje neuron death, the loss of locomotion and coordination as well as the death of the animals (Griffin et al., 2004).

These findings point to an important protective role of allopregnanolone during fetal brain development. The immature brain is indeed particularly vulnerable to deprivation. However, readers should be reminded that GABA does not function as an inhibitory neurotransmitter in immature neurons, but predominantly as a depolarizing-excitatory one (Ben-Ari, 2002; Dehorter et al., 2012). Thus, we cannot directly compare $GABA_A$ receptor modulation by allopregnanolone between the developing and adult brain.

14. Effects of progesterone and allopregnanolone on developing white matter and myelin repair

The myelin sheaths which surround axons not only improve signal transduction, as they are required for the rapid saltatory conduction of nerve impulses, but they also provide trophic support and are essential for the integrity of neuronal networks and neuron survival (Nave and Trapp, 2008). In the CNS, axons are myelinated by a particular type of glial cells, the oligodendrocytes. Myelinated axons and associated cells form the white matter, providing a structural substrate for neural circuits. In humans, oligodendrocyte maturation begins during the second trimester of gestation, progresses toward birth and continues until the end of puberty (Craig et al., 2003; Jakovcevski et al., 2009; Lebel and Beaulieu, 2011; Perrin et al., 2008). The maturation of white matter is thus a long-term process.

Stimulating myelination and protecting the white matter during development are of considerable clinical interest. Indeed, the forming white matter is particularly sensitive to injury, and in humans, a window of vulnerability exists between 23 and 32 weeks gestation for the periventricular white matter. Its damage is referred to as periventricular leukomalacia (PVL) and corresponds to the principal form of brain injury in the premature infant and the predominant pathologic finding underlying cerebral palsy (Alix, 2006). There are multiple potential causes of PVL, including premature birth, intrauterine infections, hypoxia–ischemia, neuroinflammation and axonopathies. During the period when infants are at greatest risk for PVL, the subcortical white matter is predominantly populated by immature premyelinating oligodendrocytes, which are more vulnerable than mature oligodendrocytes (Back et al., 2002; Billiards et al., 2008). Injury results in an arrest of pre-oligodendrocyte maturation, leading to myelination failure, chronic white matter damage and persistent neurological morbidity (Back et al., 2001; Billiards et al., 2008). The failure of pre-oligodendrocytes to differentiate into myelinating oligodendrocytes and the chronic disturbance of myelination in PVL is a challenging problem, as myelin has normally the capacity to regenerate via a natural healing process. It involves the proliferation, migration and differentiation of OPC, which are largely distributed throughout the CNS, even in adults (Buser et al., 2012; Franklin and FFrench-Constant, 2008). Both the great vulnerability of pre-oligodendrocytes and the elevated susceptibility of early maturing axons to hypoxic–ischemic conditions and excitotoxic insults may contribute to the white matter pathology, and both pre-oligodendrocytes and immature neurons are thus potential targets for protective and therapeutic interventions (Alix et al., 2012; Follett et al., 2004). Because of the continuous and reciprocal molecular dialog between oligodendrocytes and axons, and its role in development, maintenance and repair of the myelin sheaths and in axon integrity, neuroprotective and remyelination strategies may be considered as complementary.

The guinea pig is a precocial rodent with a gestation period of 70 days and has been proposed as a suitable model for studying the consequences of placental microvascular dysfuntion (Dyson et al., 2012). In this species, intra-uterine growth restriction caused by removing half of the placental arteries at mid-gestation resulted in decreased myelin basic protein (MBP) expression in the hippocampus, but not in cerebral cortex, when measured at 65 days of gestation. There was a marked increase in PR-A and PR-B expression in the brain of the growth restricted fetuses, suggesting increased PR-dependent actions of progesterone, which could play a role in protective mechanisms (Palliser et al., 2012).

Rats and mice are altricial species, and myelin formation in the CNS only starts after birth and is maximal between the second and third postnatal week (Bjelke and Seiger, 1989; Craig et al., 2003; Foran and Peterson, 1992). This developmental period of myelination coincides with the window of great white matter vulnerability in humans (23–32 weeks postconceptional age), when pre-oligodendrocytes are abundant and myelination starts (Craig et al., 2003). This particular stage of oligodendrocyte lineage progression may extend until postnatal day 14 for brain regions characterized by a delayed onset of myelination (Dean et al., 2011a). Based on these observations, translational *in vivo* and *in vitro* models to study the developmental vulnerability of oligodendrocytes have been proposed (Dean et al., 2011b; Follett et al., 2004; Shen et al., 2010).

A role of progesterone in oligodendrocyte maturation and developmental myelination has been demonstrated in organotypic slice cultures prepared from the cerebellum of postnatal day 7 rats and mice. These organotypic cultures offer an integrated system, which closely reproduces developmental events and they provide a unique model for studying the myelination of axons (Ghoumari et al., 2002, 2003). Adding progesterone to the culture medium accelerated the myelination of axons. This promyelinating effect of progesterone involved PR, as it could be mimicked by the very selective PR agonist promegestone and as it was no longer observed in cerebellar slices prepared from PR knockout mice (Ghoumari et al., 2003). The observation that progesterone completely failed to promote myelin formation after the genetic invalidation of PR demonstrates a key role of the receptors. However, in slices from wild-type animals, in the presence of PR, a stimulatory effect of allopregnanolone on myelination involving $GABA_A$ receptors could be observed (Ghoumari et al., 2003).

At the cellular level, allopregnanolone may stimulate the proliferation of early OPC by autocrine signaling mechanisms. The early OPC indeed synthesize significant amounts of progesterone and allopregnanolone, and the latter stimulates their proliferation. Moreover, early OPC also express $GABA_A$ receptors, which mediate the mitogenic effect of allopregnanolone (Gago et al., 2001, 2004; Schumacher et al., 2012). Other *in vitro* studies have demonstrated a role of allopregnanolone in stimulating the proliferation of neural progenitor cells, and they are consistent with the observation that the type 1 5α-reductase is first expressed within neurogenic regions of the developing brain (Lauber and Lichtensteiger, 1996). Allopregnanolone has been shown to induce the proliferation of neural stem cells isolated from rat cerebral cortex, of embryonic rat hippocampal neurons and of human neural stem cells in culture via a mechanism involving both $GABA_A$ receptors and voltage-gated L-type calcium channel (Wang et al., 2005; Wang and Brinton, 2008).

At a later time of oligodendrocyte maturation, approximately corresponding the stage of high vulnerability in humans, progesterone stimulates both the proliferation and differentiation of pre-oligodendrocytes via PR-dependent mechanisms. In fact, its mitogenic effect could be inhibited by the PR antagonist mifepristone and could not be mimicked by allopregnanolone (Ghoumari et al., 2005).

An important role of progesterone in OPC maturation has also been demonstrated in the adult male rat after spinal cord injury, resulting in the loss of oligodendrocytes and myelin. Indeed, OPC only differentiated into mature oligodendrocytes if rats were treated with progesterone (Labombarda et al., 2009). Thus, as for developmental periods of great white matter vulnerability, oligodendrocyte maturation in the adult CNS appears to be arrested after injury, but may be reactivated by progesterone. Whether the differentiating effect of progesterone on OPC reflects direct actions or is indirectly mediated via other cell types remains to be clarified. Indeed, progesterone not only stimulates the generation of new oligodendrocytes, but the hormone has also a beneficial influence on neurons, astrogliosis and neuroinflammatory responses (Labombarda et al., 2011).

Importantly, progesterone exerts myelinating, neuroprotective and anti-inflammatory actions and improves neurological outcomes in experimental autoimmune encephalomyelitis (EAE), an animal model close to multiple sclerosis in humans (Garay et al., 2007, 2009). EAE can be induced in rats or mice by direct immunization with myelin proteins or peptides (active EAE, the most commonly used model) or by the transfer of autoreactive T cells taken from animals which have been immunized against a particular myelin antigen (passive EAE) (Lassmann, 2008). Multiple sclerosis is indeed considered to be an autoimmune-mediated disease, in which the immune system attacks the myelin sheaths of the brain and spinal cord. Progesterone treatment initiated as late as two weeks after immunization with myelin protein peptide still exerted beneficial effects in EAE, suggesting a large therapeutic window that can be used (Yates et al., 2010; Yu et al., 2010). Moreover, progesterone has been shown to protect against demyelination or to promote myelin repair in different animal models of toxin-induced demyelination (Acs et al., 2009; Ibanez et al., 2004; Kipp and Beyer, 2009; Martine El-Etr, Marion Rame and Regine Sitruk-Ware, unpublished observation).

Effects of progesterone on the remyelination of axons have been tested after the demyelination of cerebellar slice cultures with lysophosphatidylcholine (LPC), which has a strong myelinolytic action (Gent et al., 1971). It should be remembered here that the term "myelination" generally refers to the developmental process, whereas the term "remyelination" is used for the formation of new myelin sheaths around demyelinated axons (myelin repair or myelin regeneration). Four days after LPC-induced demyelination, myelin immunostaining appeared sparse when slices were cultured in medium devoid of progestins. However, in slices cultured for 4 days in the presence of progesterone, there was a marked increase in myelinated axons (Hussain et al., 2011). The 19-norpregnane derivative Nestorone, which selectively targets the PR, also efficiently promoted the remyelination of axons at much lower doses. In contrast, another progestin used in contraception and hormone therapy, medroxyprogesterone acetate, had no beneficial effect on the formation of new myelin sheaths. Nestorone was also shown to stimulate the proliferation, migration and differentiation of OPC. The remyelinating action of Nestorone required the presence of PR, as it was observed in cerebellar slices taken from wild-type mice, but not in those from PR knockout mice (Hussain et al., 2011).

Alterations in the synthesis of progesterone and allopregnanolone within the brain may also play a role in demyelinating diseases such as multiple sclerosis. Thus, a recent study has demonstrated the induction of 3 micro-RNAs (miR-338, miR-155 and miR-491), specific for neurosteroid synthesis enzymes, in the brains of patients with multiple sclerosis (Noorbakhsh et al., 2011). Analysis of the neurosteroidogenic pathways inhibited by micro-RNAs revealed suppression of enzyme transcripts and protein levels as well as reduced levels of allopregnanolone in white matter. Importantly, diminished expression of neurosteroidogenic enzymes and brain allopregnanolone was also observed in mice with EAE, and their treatment with allopregnanolone limited neuroinflammation, myelin damage and axonal injury and improved neurological outcomes (Noorbakhsh et al., 2011).

Studies presented in this section show that both progesterone signaling via PR and allopregnanolone signaling via $GABA_A$ receptors exert a marked influence on OPC proliferation, their differentiation and myelin formation. Although results are provided by a series of independent observations, we hypothesize that allopregnanolone may regulate the proliferation of early progenitors. In contrast, at later stages, PR may play a particularly important role in myelin formation. Indeed, the myelinating and remyelinating effects of progesterone are no longer observed in PR knockout mice.

Although the focus of this review is on the CNS, it is worth mentioning here that progesterone and allopregnanolone also drive myelination in peripheral nerves, where axons are myelinated by Schwann cells. Earlier studies have provided evidence that PR play an important role in myelination and remyelination within the peripheral nervous system (PNS) (Chan et al., 1998; Koenig et al., 1995; Sereda et al., 2003). Interestingly, it has been proposed that progesterone may regulate myelin formation by activating transcription via neuronal PR (Chan et al., 2000). Since then, the picture has become even more complex, with the demonstration of a direct modulation of peripheral myelin protein gene expression by progesterone and allopregnanolone in rat Schwann cells. Thus,

expression of the peripheral myelin protein zero (P0 or MPZ) is increased by progesterone and 5α-DHP treatment in the sciatic nerve and in cultured Schwann cells. On the contrary, the expression of peripheral myelin protein-22 (PMP22) was found to be stimulated by allopregnanolone acting via $GABA_A$ receptors (Melcangi et al., 1999, 2003, 2005).

15. Neuroprotective effects of progesterone during adulthood

As discussed above (Section 13), elevated levels of progesterone and allopregnanolone are protective for the developing brain. Features of development are often recapitulated, although not entirely, when adult neural cells respond to injury or degeneration and during repair processes (Chen et al., 2005; Fancy et al., 2011). Levels of progesterone are indeed upregulated after CNS injury, as documented in experimental animal models and in TBI patients, and it has been proposed that endogenous progesterone may participate in neuroprotective and neuroregenerative mechanisms (De Nicola et al., 2009; Schumacher et al., 2007b; Wagner et al., 2011). Boosting this natural response to injury by the repeated administration of high doses of progesterone has been shown to exert beneficial effects on neuron viability and myelin repair in a variety of experimental animal models.

Twenty years ago, the team of Donald Stein reported that female rats are protected against TBI-induced brain damage (neuron death and edema) by their elevated endogenous levels of progesterone. Protective effects were particularly pronounced in pseudopregnant female rats with high levels of progesterone (Roof et al., 1993). They then showed that treatment with progesterone also reduces neuronal loss and facilitates cognitive recovery in male rats after focal bilateral TBI (Roof et al., 1994). Prolonged administration of progesterone led to more complete recovery after TBI (Cutler et al., 2006; Galani et al., 2001). It is also important to avoid a too rapid withdrawal from progesterone, as this may exacerbate ischemic damage and cause increased anxiety, seizure susceptibility and excitotoxicity (Cutler et al., 2005). Particularly intriguing and encouraging was the finding that progesterone is effective in reducing edema and brain damage in rats of both sexes when treatment was delayed as much as 24 h after injury (Roof et al., 1996). The transient increase in endogenous brain progesterone in response to brain injury may contribute to this extended therapeutic window (Meffre et al., 2007).

A variety of mechanisms have been proposed underlying the neuroprotective effects of progesterone, including reduction in brain edema (Guo et al., 2006; Roof et al., 1994); anti-inflammatory effects (Grossman et al., 2004; He et al., 2004a); anti-oxidant activity (Djebaili et al., 2005), preservation of mitochondrial functions (Robertson et al., 2006; Sayeed et al., 2009); regulation of hemostatic proteins (Vanlandingham et al., 2008), attenuation of blood–brain barrier dysfunction (Ishrat et al., 2010) and promotion of the survival of newborn neurons (Zhang et al., 2010). However, the signaling mechanisms involved in the protective effects of progesterone have only started to be explored (Cai et al., 2008). The prevailing view is that the neuroprotective actions of progesterone after TBI may be mainly mediated by its metabolite allopregnanolone. This assumption is based on studies showing that the effects of progesterone can be mimicked by treatment with allopregnanolone (Djebaili et al., 2004; He et al., 2004b; Sayeed et al., 2009). An intriguing observation was that the enantiomer of progesterone has also neuroprotective effects after TBI (Vanlandingham et al., 2006). This was an unexpected finding, as both the transcriptional actions of PR and the modulation of $GABA_A$ receptors by allopregnanolone show enantioselectivity (Covey, 2009). There remains of course the possibility of an alternative neuroprotective pathway of the enantiomer of progesterone (Maller, 2001).

Neuroprotective effects of progesterone have also been particularly well demonstrated after middle cerebral artery occlusion (MCAO) in rats and mice, an experimental model of stroke. In this model, blood flow through the medial cerebral artery is interrupted either transiently during 1–2 h followed by reperfusion, or permanently. Both types of MCAO result in severe ipsilateral brain damage and neuron death. At about the same time as Donald Stein and collaborators reported neuroprotective effects of progesterone after TBI, they also demonstrated that administration of progesterone reduces brain damage in male rats when administered prior to transient MCAO or at the time of reperfusion (Jiang et al., 1996). Later, progesterone was also shown to improve neurological outcomes after MCAO in male mice (Gibson and Murphy, 2004).

Whereas it is quite common to perform meta-analyses of clinical studies, systematic reviews of translational animal studies are unfortunately rare. A serious limitation for meta-analyses of animal studies is the fact that negative results are less likely to be published. Recently, a systematic review of animal studies has been published investing the neuroprotective effects of progesterone treatment after TBI or cerebral ischemia. This meta-analysis provided supporting evidence for a neuroprotective role of progesterone in both disorders (Gibson et al., 2008).

Since this report, the neuroprotective actions of progesterone continued to be investigated in a series of experimental stroke studies, which have produced additional important information. As stroke is an age-related disorder, becoming increasingly common among older individuals, it was important to experimentally demonstrate that progesterone continues exerting protective effects after MCAO in middle-aged and aged animals. Treatment with progesterone indeed improved neurological outcomes and inflammatory responses following cerebral ischemia in reproductively aging female mice (12-month old) and in middle-aged and very old (24-month old) male rats (Gibson et al., 2011; Wang et al., 2010a; Yousuf et al., 2013). Moreover, progesterone treatment provides long-term protection, verified for a period up to 2 weeks post-MCAO, for both males and females, with a therapeutic window of at least 6 h (Dang et al., 2011; Gibson et al., 2008; Ulbrich et al., 2012). Treatment with progesterone or estradiol alone or co-treatment with both hormones reduced ischemic damage after MCAO in male and female rats, which responded comparably to hormonal protection (Dang et al., 2011; Ulbrich et al., 2012). Thus, progesterone may now be considered to be ready for neuroprotective trials in patients with ischemic stroke.

As for TBI, allopregnanolone has been proposed to mediate the neuroprotective effects of progesterone after cerebral ischemia. This assertion was supported by the observation that for a same dose, the administration of allopregnanolone was more potent than progesterone in attenuating cerebral damage after MCAO (Sayeed et al., 2006). Moreover, allopregnanolone, but not progesterone, was shown to inhibit the activity of the mitochondrial permeability transition pore, a key player in neuronal apoptosis (Sayeed et al., 2009). Treatment with either progesterone or allopregnanolone was also efficient in attenuating dysfunctions of the blood–brain barrier and in reducing neuroinflammatory responses (Ishrat et al., 2010).

Allopregnanolone has been shown to participate in the neuroprotective effect of progesterone in other models of neuroinjury. Thus, in an *in vivo* experimental system of excitotoxic cell death, progesterone administration increased the levels of 5α-DHP and allopregnanolone within the hippocampus and prevented kainic-acid-induced neuronal loss. Administration of the 5α-reductase inhibitor finasteride abolished the neuroprotective effect of progesterone, consistent with an important role of its metabolites (Ciriza et al., 2004). More recently, allopregnanolone formation in the hippocampus was shown to protect neurones

from tributyltin-induced neurotoxicity via a mechanism involving $GABA_A$ receptors (Ishihara et al., 2013).

The therapeutic efficacy of allopregnanolone for providing neuroprotection and promoting repair processes within the hippocampus has been demonstrated in normal aging mice and in a transgenic mouse model of Alzheimer's disease (3xTgAD mice) (Brinton, 2013). In the 3xTgAD mice, the regenerative potential of neural stem cells rapidly decreases during aging, and neurogenesis is severely impaired. If started sufficiently early, allopregnanolone treatment can stimulate neurogenesis and survival of newly generated cells within the hippocampus of these mice, and most importantly, restore learning and memory functions (Singh et al., 2012; Wang et al., 2010a,b). Allopregnanolone treatment also increased expression of the 2′,3′-cyclic-nucleotide 3′-phosphodiesterase (CNPase), a specific marker of oligodendrocytes (Chen et al., 2011). This is an interesting observation, as white matter degeneration is an early event in the pathophysiology of Alzheimer's disease (Bartzokis, 2011; Ringman et al., 2007). Moreover, allopregnanolone significantly reduced the generation of amyloid-β peptide and neuroinflammatory responses (Chen et al., 2011).

16. Neuroprotective effects of progesterone: the allopregnanolone hypothesis revisited

For the above described neuroprotective and neuroregenerative responses, allopregnanolone has been proposed to mediate the neuroprotective effects of progesterone. At the basis of this assertion is the therapeutic efficacy of treatments with allopregnanolone. However, a possible role of PR in mediating protective and trophic effects of progesterone and allopregnanolone on the brain had not been considered.

A recent study has cast a new light on the role of PR in endogenous neuroprotective mechanisms after ischemic stroke. The first indication for an important role of PR was the observation that levels of its ligands progesterone and 5α-DHP, but not those of allopregnanolone, were strongly and transiently upregulated 6 h after MCAO in the brain of adult male mice. In response to ischemic injury, brain levels of progesterone plus 5α-DHP nearly reached "pregnancy levels" (about 200 nM) in the male brain, whereas levels of allopregnanolone remained in the low nanomolar range (Liu et al., 2012) (Fig. 3). It is important to specify here that steroid analysis was performed by GC/MS preceded by an improved tissue extraction method (Liere et al., 2009).

The use of PR knockout mice then allowed the demonstration that PR deficiency in knockout mice ($PR^{-/-}$ mice), or even the loss of a single allele of the *PR* gene in heterozygous knockout mice ($PR^{+/-}$ mice), markedly increases the susceptibility of the brain to ischemic damage, thus indicating that PR expression may be limiting for the neuroprotective efficacy of endogenous brain progesterone. The greater resistance of wild-type mice to ischemic lesions was observed 24 h after MCAO, but no longer after 48 h. A possible explanation for the transient protection is that the marked and transient increase in endogenous brain progesterone may have provided a time-limited neuroprotection via PR. Reducing the extent of brain tissue damage and the impairment of motor functions for a longer period of time, up to 48 h, required the administration of exogenous progesterone (Liu et al., 2012). Again, progesterone therapy was not protective in PR knockout mice, consistent with a key role of PR (Liu et al., 2012). In this study, a commonly used dose of progesterone was administered (8 mg/kg), which produces pregnancy levels of the hormone 2 h after its administration.

Treatment with the same dose of allopregnanolone reduced infarct volume and improved functional outcomes 48 h after MCAO not only in wild-type, but also in PR knockout mice. This finding shows that administration of allopregnanolone can protect the brain against ischemic damage by signaling mechanisms which are not involving PR (Liu et al., 2012). However, it can be concluded that endogenous conversion of progesterone to allopregnanolone is not sufficient for efficient neuroprotection, otherwise the administration of a high dose of progesterone would have reduced

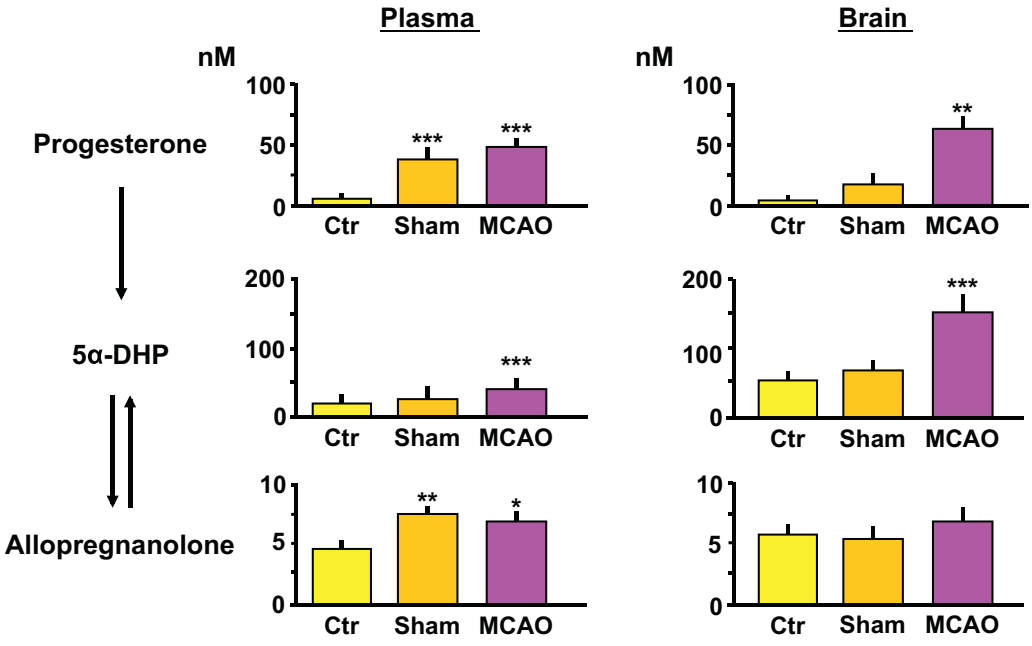

Fig. 3. Measures of plasma and brain levels of progesterone, 5α-dihydroprogesterone (5α-DHP) and allopregnanolone performed by GC/MS in male mice 6 h after middle cerebral artery occlusion (MCAO). Plasma levels of progesterone and allopregnanolone are significantly increased in response to surgical stress (sham operation). Concentrations of progesterone and 5α-DHP are strongly and specifically increased in response to MCAO within the brain (ipsilateral + contralateral sides), where they nearly reach "pregnancy levels". Asterisks denote statistical differences when compared to the control groups by Newman–Keuls tests after ANOVA.
Data from Liu et al. (2012).

infarct volume and improved neurological outcomes not only in wild-type, but also in PR knockout mice. Consistent with this interpretation of the results, brain levels of allopregnanolone were not upregulated in response to MCAO (Liu et al., 2012). Taken together, these results point to a key role of PR in neuroprotective mechanisms, as already shown for the myelinating and remyelinating actions of progesterone (see Section 14), and they identify PR as an important therapeutic target for neuroprotective interventions after stroke. Indeed, the potent progestin Nestorone, which selectively activates PR, protected the brain against ischemic damage and improved functional outcomes at a very low dose (0.08 mg/kg) (Liu et al., 2012).

In addition to experimental models of TBI and ischemic stroke, progesterone has been shown to markedly improve the viability of motoneurons after transection of the rat spinal cord and in the Wobbler mouse, a mouse model of spontaneous spinal motoneuron degeneration (De Nicola et al., 2009; Labombarda et al., 2003; Meyer et al., 2010). The respective roles of PR and allopregnanolone signaling in the protective effects of progesterone on motoneurons were evaluated in organotypic spinal cord slice cultures exposed to traumatic injury (Krassioukov and Weaver, 1995). Adding progesterone to the culture medium at the time of injury significantly limited cell membrane damage and motoneuron death (Labombarda et al., 2013). The neuroprotective effects of progesterone were not inhibited by the 5α-reductase inhibitor finasteride and they involved PR, as they could not be observed in slices from PR knockout mice. Interestingly, as for experimental stroke, allopregnanolone was neuroprotective for slices from wild-type and PR knockout mice. This observation confirmed a PR-independent neuroprotective effect of allopregnanolone, which involved $GABA_A$ receptors as it could be blocked by gabazine (Labombarda et al., 2013).

17. Progesterone receptor haploinsufficiency

The use of PR deficient knockout mice has revealed a key role of the receptor in the facilitation of female reproductive behavior by progesterone and in the myelinating, remyelinating and neuroprotective effects of the hormone. The loss of a single allele of the *PR* gene in heterozygous knockout mice ($PR^{+/-}$ mice) resulted in decreased PR expression: specific binding of [^{3}H]promegestone to PR was decreased by 40–50% in the hypothalamus and by 50–60% in the uterus (Lydon et al., 1995; Mani et al., 1997). Correspondingly, analysis of PR mRNA levels by quantitative PCR showed that PR mRNA expression is absent in $PR^{-/-}$ mice and reduced by about 60% in cerebral cortex, subcortical regions and hypothalamus of $PR^{+/-}$ mice (Liu et al., 2012). In spite of this significant reduction in PR expression, no particular phenotype was observed in the $PR^{+/-}$ mice for reproductive functions, and the heterozygous females displayed lordosis responses comparable to the wild-types (Mani et al., 1997). This result is consistent with earlier studies showing that activation of part of the hypothalamic PR is sufficient for the induction of sexual receptivity in female rats. A nuclear PR exchange assay indeed allowed the estimation that translocation of only a small percentage of cytoplasmic PR into the nucleus after estrogen priming or during proestrus (about 20% to 30%) is sufficient for the activation of lordosis behavior (Parsons et al., 1981a; Rainbow et al., 1982a). Moreover, the threshold level of estrogen-inducible hypothalamic PR necessary for the appearance of sexual receptivity is similarly low (25% to 35% of maximal induction) (Parsons et al., 1980).

In contrast, levels of PR expression appear to be limiting for non-reproductive functions of progesterone, as has been demonstrated for its myelinating, remyelinating and neuroprotective effects. For these functions, PR heterozygous mice show altered responses to progesterone: the hormone fails to stimulate myelin formation and $PR^{+/-}$ mice show significantly increased sensitivity to ischemic brain damage (Ghoumari et al., 2003; Hussain et al., 2011; Liu et al., 2012) (Fig. 4). These examples of PR haploinsufficiency provide further evidence for a key role of PR in mediating the myelinating and neuroprotective actions of progesterone.

18. Therapeutic options for progestogens in neuroprotection and myelin repair

When considering the therapeutic use of progestogens for neuroprotection or myelin repair, a first decision to be taken is whether to use progesterone or one of the numerous progestins, which have been developed for contraception or hormone therapies. Interestingly, progesterone has been used in the recent phase II trials in TBI patients, either administered intravenously or by intramuscular injections (Wright et al., 2007; Xiao et al., 2008). Moreover, two ongoing large phase III trials, respectively named "SyNAPSe" and "ProTECT III" are testing the protective effects of intravenous progesterone in TBI patients (see the corresponding web sites). The choice of using progesterone instead of progestins in these trials may have been motivated by the prevailing view that neuroprotective effects of progesterone may be mediated by allopregnanolone. Most progestins are indeed not converted to this $GABA_A$ receptor active natural metabolite. Moreover, progesterone and its metabolites can bind to a variety of receptors in the nervous system, in addition to PR, which are not necessarily activated by progestins. For example, steroids which are potent PR agonists or antagonists, including promegestone, norethisterone, norgestrel and mifepristone do not bind to the α-isoform of the mPR (membrane progesterone receptors, which are distinct form classical intracellular PR) (Thomas et al., 2007). Thus, progesterone has a much wider range of actions than progestins and can be expected to offer more benefits.

Epidemiological studies have also provided evidence that progesterone may offer a better benefit/risk ratio than synthetic progestins, but this may only be relevant for long-term treatments. Thus, results of cohort studies have shown that in contrast to postmenopausal hormone replacement therapy (HRT) with progestins, the use of natural micronized progesterone is not associated with an increase in breast cancer or thrombotic risk (Banks et al., 2003; Canonico et al., 2010, 2011; Fournier et al., 2005, 2009; Gompel, 2012; Scarabin et al., 2011; Stanczyk et al., 2013).

The use of progesterone for neuroprotective and remyelinating treatments raises the important question of its mode of administration. Orally, progesterone can only be taken in a micronized form as the hormone is poorly absorbed and is metabolized during the first hepatic pass (de Lignieres, 1999). However, even when micronized, oral progesterone has low bioavailability (<5%) and a short half-life (about 16 h) (Simon et al., 1993; Stanczyk et al., 2013). Moreover, circulating levels of progesterone achieved after oral administration of micronized progesterone may have been overestimated by radioimmunological measurements, as a comparative analysis with liquid chromatography–mass spectrometry (LC–MS) has reported significantly lower concentrations (Levine and Watson, 2000). Nevertheless, oral micronized progesterone, given at rather high doses of 200 mg per day, has clinical potential for the treatment of specific endocrine problems and is an efficient postmenopausal HRT component (Fitzpatrick and Good, 1999; Goletiani et al., 2007).

However, the efficient use of progesterone in neuroprotective therapies is likely to require the rapid induction of elevated brain levels of the hormone. This may be achieved by administering progesterone via intravenous, transdermal, vaginal, rectal and intranasal routes or by intramuscular injections (Goletiani et al.,

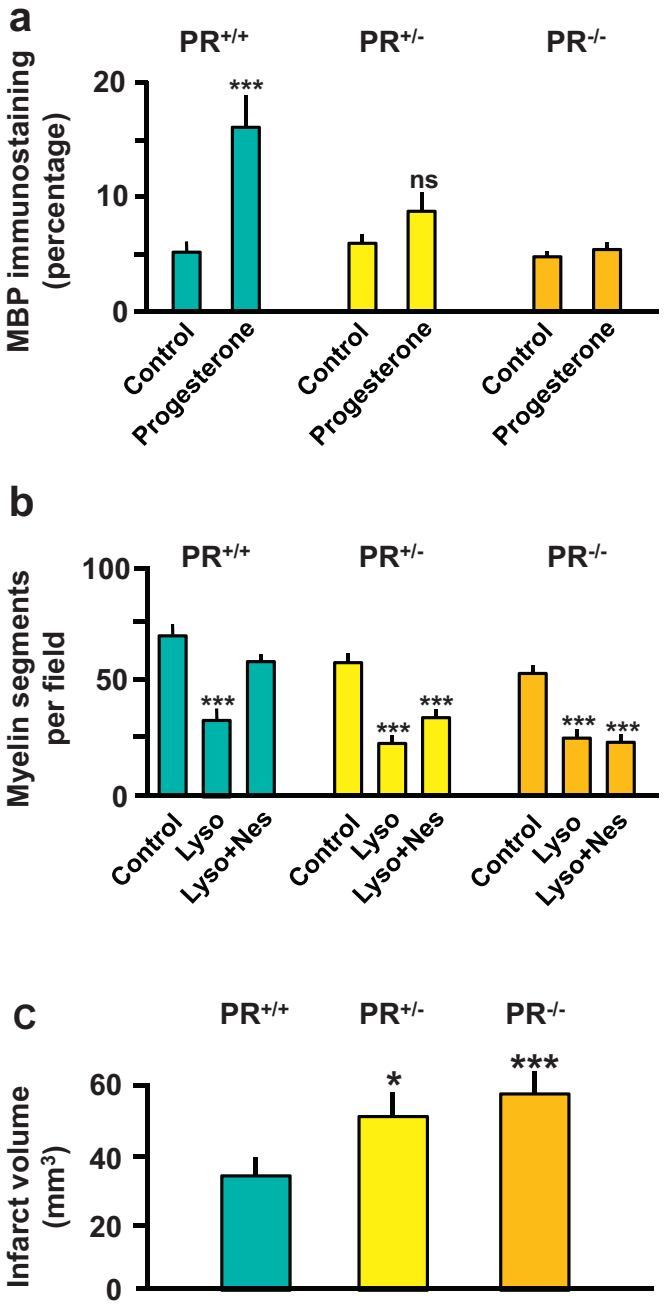

Fig. 4. Intracellular progesterone receptors (PR) are limiting factors for the promyelinating and neuroprotective effects of progesterone. Examples of PR haploinsufficiency for non-reproductive brain functions of progesterone. (a) Role of PR in developmental myelination in organotypic cultures of cerebellar slices taken from postnatal day 7 mice and cultured in the absence (control) or presence of progesterone (20 μM). Myelination was quantified by analyzing myelin basic protein (MBP) immunostaining ($PR^{+/+}$ = wild-type mice expressing functional PR; $PR^{-/-}$ = homozygous PR knockout mice; $PR^{+/-}$ = heterozygous mice for which PR expression is decreased by 50–60%). Progesterone treatment does not significantly accelerate myelination in $PR^{+/-}$ mice with reduced PR expression. (b) Role of PR in stimulating myelin repair by Nestorone (Nes, 20 μM) after lysolecithin (Lyso) induced demyelination of cerebellar slices taken from postnatal day 10 mice. As in (a) for myelination, myelin repair is not stimulated in $PR^{+/-}$ mice with reduced PR expression. (c) Role of PR disruption on the total brain infarct volume 24 h after middle cerebral artery occlusion (MCAO) in male mice. Lack of PR ($PR^{-/-}$ mice) or reduced PR expression ($PR^{+/-}$ mice) increase the sensitivity of the brain to ischemic damage. Asterisks denote statistical differences when compared to the respective controls (a and b) or to $PR^{+/+}$ wild-type mice (c) by Newman–Keuls tests after ANOVA (ns: non-significant).
Data from Ghoumari et al. (2003), Hussain et al. (2011) and Liu et al. (2012).

2007). The recent trials in TBI patients have opted for intramuscular injection (Xiao et al., 2008) or intravenous infusion of progesterone (Wright et al., 2007) (and the ongoing phase III trials). The intramuscular route can be associated with an interesting depot effect, which prolongs the elevation of progesterone levels (Nillius and Johansson, 1971). New aqueous preparations of progesterone have become available for efficient subcutaneous administration, less painful than oily intramuscular formulations (de Ziegler et al., 2013). The intravaginal route is an alternative and very efficient mode for the administration of the hormone (de Ziegler and Fanchin, 2000; Stanczyk et al., 2013).

The intranasal route of progesterone administration has again moved to the center of interest for easy, rapid and efficient parenteral delivery of progesterone to the brain. A recent proof of concept study has indeed shown that intranasally administered progesterone rapidly accumulates within specific brain regions, in particular in hippocampus, hypothalamus and striatum, and exerts anxiolytic effects (Ducharme et al., 2010). Another study has reported that intranasal administration of progesterone rapidly enhances dopamine levels within specific brain regions (de Souza Silva et al., 2008). It is interesting to mention here that the intranasal route also allows the efficient delivery to the brain of other natural steroid hormones, such as testosterone, as demonstrated in experimental animals and humans (Mattern et al., 2008; Tavares et al., 2007; Topic et al., 2007; van Wingen et al., 2009).

Another important question is whether progesterone needs to be administered for prolonged periods of time, or whether repeated short-term administrations would be more efficient. The temporally dynamic patterns of the interactions between PR and chromatin, and the pulsatile fluctuations, daily rhythms and cyclic changes in endogenous progesterone suggest that the timing of progesterone administration may be crucial for an efficient hormone treatment, and argue against continuous administration. An influence of the treatment paradigm has indeed been shown in two recent studies. In the brains of transgenic mice modeling Alzheimer's disease, estradiol therapy for 3 months reduced the accumulation of β-amyloid protein. Whereas continuous co-administration of progesterone inhibited the beneficial effect of estradiol, a discontinuous progesterone treatment regimen potentiated its effect (Carroll et al., 2010). Continuous or seuential administrations of progesterone were also shown to induce different gene expression profiles within the female rat hippocampus (Zhao et al., 2012). However, we have no information concerning the effects of traumatic injuries on endogenous rhythms of progesterone and its receptors. On the other hand, the developing nervous system is exposed to constantly elevated levels of progesterone. Moreover, PR are not down-regulated by progesterone in most brain regions outside the hypothalamus, providing support for the efficacy of sustained progesterone therapy. Unfortunately, as treatment paradigms used in most translational animal studies are very similar to each other, using comparable hormone dosing and timing of administration, we do not have sufficient experimental information for optimizing progesterone treatments.

Alternatively, the observation that PR play a key role in the neuroprotective and remyelinating effects of progesterone, offers new therapeutic options for the use of progestins which selectively target PR. Moreover, two experimental studies have demonstrated that administration of a potent and PR selective agonist, such as the 19-norpregnane derivative Nestorone, is sufficient for efficient stimulation of remyelination and neuroprotection (Hussain et al., 2011; Liu et al., 2012). In addition to their selective actions, the high potency of some progestins may allow their sustained administration at low doses via appropriate release devices (Sitruk-Ware and Nath, 2010).

For the recently completed Popartmus trial, the choice was to orally administer the 19-norpregnane derivative nomegestrol acetate (10 mg/day) in combination with transdermal estradiol (75 μg once a week) to prevent postpartum relapses in women with multiple sclerosis (Vukusic et al., 2009). The study has recently been completed, unfortunately without reaching the expected number of probands, and outcomes did not show a beneficial effect of the treatment. It is clear that attempting to prevent relapses in multiple sclerosis has nothing to do with myelin repair strategies, but rather concerns the modulation of immune responses. In the EAE model of multiple sclerosis, the effects of progesterone on immunological parameters have only been addressed in one study and they need to be defined (Yates et al., 2010). Moreover, the impact of progesterone and progestins on the different components of the immune system are complex and still poorly understood (Hughes, 2012). It is also important to be aware that different types of progestins commonly used in contraception and postmenopausal HRT have different effects depending on their steroid receptor interactions. For example, PR-selective 19-norpregnane derivatives will not affect immune functions and T-cells in the same manner as progestins which also activate the glucocorticoid receptor, and are unlikely to prevent T-cell activation (Tomasicchio et al., 2013).

These observations highlight the fact that not all progestins display the same effects and efficiency. Differences in the pharmacological characteristics, mechanisms of actions and clinical effects of different progestins have been extensively reviewed recently (Stanczyk et al., 2013). Progestins are used instead of progesterone because of their greater bioavailability, half-life and potency for the treatment of a variety of endocrine disorders, fertility problems, contraception and postmenopausal HRT. Although synthetic progestins have been designed to signal through PR, many of them also bind to other nuclear receptors within target tissues, in particular the androgen receptor and the glucocorticoid receptor (Moore et al., 2012; Stanczyk et al., 2013). Thus, progestins derived from 19-nortestosterone (norethisterone, gestodene, levonorgestrel, norgestrel and norethindrone) show agonistic activity on the androgen receptor. The progesterone derivative medroxyprogesterone acetate has agonistic activity on both androgen and glucocorticoid receptors and can block the actions of estradiol in the nervous system (Littleton-Kearney et al., 2005; Moore et al., 2012; Nilsen and Brinton, 2002, 2003; Pazol et al., 2004). This cross-talk of progestins to receptors other than PR may have important consequences for their actions, by generating undesirable side effects and risks.

Important efforts have been made for a decade to produce progestins which more selectively target the PR and with less side-effects. This is the case for the 19-norpregnane derivatives, which bind almost exclusively to PR and do not interfere with the other steroid receptors. They include promegestone, nomegestrol acetate and Nestorone, which have been mentioned throughout this review (Sitruk-Ware, 2008). Whereas nomegestrol acetate, tested in the Popartmus trial, can be taken orally, this is not the case for Nestorone, one of the most potent and selective progestins. For this reason, Nestorone has to be administered parenterally (Mueck and Sitruk-Ware, 2011; Sitruk-Ware and Nath, 2010).

19. Conclusions and perspectives

This journey through the different sources of progesterone and allopregnanolone, their multiple and complex mechanisms of action and their pleiotropic effects on the brain affecting reproductive and non-reproductive function, has revealed the multiple facets of this hormone. The review has specifically addressed the roles of progesterone and allopregnanolone in modulating female reproductive behavior (lordosis response), stress responsiveness and anxiety-like behaviors and in promoting the viability of neurons and the formation of myelin. Of course, progestogens exert many other effects on the brain, involving PR signaling or the modulation of $GABA_A$ receptors by allopregnanolone. The multiple effects of progesterone and allopregnanolone are summarized in Table 1, which is not exhaustive.

Progesterone is produced by the adrenal glands and synthesized within the nervous system of both males and females throughout life, and the only difference between sexes is that males, in contrast to females, do not experience the temporary important increases in progesterone levels associated with the ovarian cycle and pregnancy. Moreover, PR are present in the nervous system of both sexes. However, we still know little about the significance of progesterone in men, and the hormone has been qualified as the "forgotten hormone in men" (Oettel and Mukhopadhyay, 2004). As progesterone and allopregnanolone are produced by the adrenal glands under the control of ACTH and within the brain, it is not further surprising that they play an important role in the modulation of stress responsiveness and anxiety in both sexes. The anxiolytic effects of progesterone are mainly mediated by its metabolite allopregnanolone and involve the modulation of synaptic and extra-synaptic $GABA_A$ receptors, as has been demonstrated in different experimental paradigms and in mice deficient of PR.

A second important role of progesterone in the nervous system of both sexes concerns the viability of neurons and the regeneration of myelin after injury. The neuroprotective and remyelinating effects of progesterone have been demonstrated in a variety of animal models and have provided the experimental basis for recent clinical trials. According to a widely accepted concept, the neuroprotective effects of progesterone may be mainly mediated by its metabolite allopregnanolone. However, the use of PR knockout mice and of selective PR agonists has allowed the demonstration that the classical intracellular receptors play a crucial role in both the neuroprotective and remyelinating actions of progesterone. These findings pave the way for new therapeutic indications of progestins designed to target the PR and already used as contraceptives, for the treatment of endocrine disorders and in postmenopausal HRT. In contrast to the more potent and selective progestins, progesterone offers the advantages of being converted to biologically active metabolites and to interact with a broader range of targets, including neurotransmitter and membrane progesterone receptors. The use of progesterone of course raises the problem of its mode of administration. Intranasal application may offer a very promising option for the delivery of progesterone to the brain.

A very interesting observation is that brain and spinal cord levels of progesterone and 5α-DHP, both ligands of the PR, are markedly upregulated in response to injury. This has been particularly well demonstrated after ischemic injury in male mice, when progesterone and 5α-DHP, but not allopregnanolone, reach levels in the male brain which are comparable to those observed during pregnancy in females. After TBI, circulating levels of progesterone are also significantly and transiently upregulated in men. This increase in progesterone in response to injury points to a physiological response by which neural cells cope with injury. As a consequence, neuroprotective treatments with progesterone may simply be a means of boosting natural endogenous protective and healing processes, which are obviously not always sufficient for efficient neuroprotection and regeneration.

Although a major aim of the present review was to highlight the key role of the classical intracellular PR in mediating neuroprotective and remyelinating effects of progesterone, the importance of the modulatory effects of allopregnanolone should not be underestimated. An important role of allopregnanolone in regulating vital neural functions via the modulation of $GABA_A$

Table 1
Effects of progesterone on the nervous system via its classical intracellular receptors (PR), and of allopregnanolone, via its positive modulation of GABAA receptors. Only part of the functional responses presented in this table are discussed in the main text. The aim of this table is to provide a comprehensive overview, while it does not claim to be exhaustive.

Functional responses	Progesterone signaling expected via PR: experimenrfal evidence	Allopregnanolone signaling via $GABA_A$ receptors: experimental evidence	References
Lordosis behavior	Time course of the induction of hypothalamic PR and behavioral sensitivity to progesterone.		Blaustein and Feder (1979) and Parsons et al. (1980)
	Infusion of PR antisense DNA into the hypothalamus.		Mani et al. (1994) and Ogawa et al. (1994)
	Progesterone does not facilitate lordosis in estrogen-primed PR knockout female mice.		Lydon et al. (1995) and Frye et al. (2006b)
	A role of both PR-A and PR-B isoforms (antisense oligonucleotides and knockouts).		Mani et al. (2006) and Guerra-Araiza et al. (2009)
		Allopregnanolone facilitates lordosis in PR knockout mice.	Frye et al. (2006b)
		Pharmacological inhibitors.	Petralia et al. (2005)
Stress responses	Modulation of stress-responsive genes.	Modulation of stress-responsive genes.	Patchev et al. (1994) and Patchev and Almeida (1996)
		Time-dependent changes allopregnanolone levels and $GABA_A$ receptor function.	Barbaccia et al. (1996)
		Pharmacological inhibitors.	Barbaccia et al. (1997, 2001)
Anxiolytic effects		Pharmacological treatments.	Bitran et al. (1995), Brot et al. (1997) and Rupprecht et al. (2009)
		Progesterone and allopregnanolone have anxiolytic effects in PR knockout mice.	Reddy et al. (2005) and Frye et al. (2006a)
Antidepressant effects		Effects of antidepressants on enzymes involved in allopregnanolone synthesis.	Griffin and Mellon (1999)
		Effects of antidepressants on nervous system and plasma allopregnanolone levels.	Uzunov et al. (1996), Romeo et al. (1998) and Ströhle et al. (1999)
		Intracerebral administration of allopregnanolone.	Molina-Hernandez et al. (2005), Majewska (1992), Rodriguez-Landa et al. (2009) and Shirayama et al. (2011)
Anesthetic effects		Progesterone and allopregnanolone exert anesthetic effects in PR knockout mice.	Reddy and Apanites (2005) and Reddy and Zeng (2007)
		Pharmacological inhibitors.	Korneyev and Costa (1996)
		Electrophysiological studies.	Harrison and Simmonds (1984) and Belelli et al. (1999)
Sleep		Effects of allopregnanolone administration and pharmacological treatments.	Lancel et al. (1997, 1999)
		Brain substrates for the effects of allopregnanolone on sleep-dependent memory functions.	Darnaudery et al. (1999) and George et al. (2010)
Anticonvulsant effects	Pharmacological suppression of hippocampal electrical activity by PR ligands.		Edwards et al. (2000)
		Anticonvulsant activity of progesterone and allopregnanolone in PR knockout mice.	Reddy et al. (2004)
		Treatments with allopregnanolone or pharmacological inhibitors.	Concas et al. (1996), Kokate et al. (1999) and Reddy and Rogawski (2001)
Antalgesic effects	Effect of intrathecal administration of PR antagonist.		Kondo et al. (2006)
		Increased allopregnanolone levels, enhanced enzymatic activities, pharmacological inhibitors.	Patte-Mensah et al. (2004b), Meyer et al. (2008) and Sasso et al. (2012)
		Local administration and modulation of endogenous allopregnanolone.	Pathirathna et al. (2005) and Aouad et al. (2009)
		Electrophysiological recordings.	Keller et al. (2004) and Poisbeau et al. (2005)
Addiction	Increased expression and transcriptional activity of striatal PR in response to cocaine.		Wu et al. (2006)
		Allopregnanolone blocks the escalation of cocaine self-administration.	Ramaker et al. (2012) and Anker et al. (2010)
		Specific actions of alcohol involve brain allopregnanolone.	Van Doren et al. (2000), Ford et al. (2008) and Tokuda et al. (2011)
		Modulatory effect of allopregnanolone on alcohol dependence and withdrawal.	Finn et al. (2004, 2008)
Development of the central nervous system	Maturation of Purkinje neurons blocked by mifepristone, and not mimicked by allopregnanolone.		Sakamoto et al. (2001, 2002)
	Progesterone does not accelerate developmental myelination in the cerebellum of PR knockout mice.		Ghoumari et al. (2003)
	Stimulation of myelination by promegestone and inhibition by mifepristone.		Ghoumari et al. (2003, 2005)

Table 1 (*Continued*)

Functional responses	Progesterone signaling expected via PR: experimenrfal evidence	Allopregnanolone signaling via $GABA_A$ receptors: experimental evidence	References
	Stimulation of myelin repair in organotypic cultures of cerebellar slices by Nestorone, no effect in PR knockout mice.		Hussain et al. (2011)
		Stimulatory effect of allopregnanolone on myelination involving $GABA_A$ receptors.	Ghoumari et al. (2003)
		Allopregnanolone stimulates the proliferation of early OPC, an effect mediated by $GABA_A$ receptors.	Gago et al. (2001, 2004)
		Allopregnanolone stimulates the proliferation of neural progenitors from embryonic rat hippocampus, and of human neural stem cells, via $GABA_A$ receptors.	Wang et al. (2005) and Wang and Brinton (2008)
		Development of neuronal connections in the rat cerebral cortex.	Grobin et al. (2003, 2006)
Neuroprotection in the developing central nervous system		Protection of the embryonic sheep brain against acute hypoxic stress.	Hirst et al. (2006) and Yawno et al. (2007)
		Allopregnanolone alleviates developmental neurodegeneration in a mouse model of Nieman-Pick type C disease.	Griffin et al. (2004) and Langmade et al. (2006)
	Intra-uterine growth restriction results in increased PR-A and PR-B expression in the guinea pig brain.		Palliser et al. (2012)
Myelination and remyelination in peripheral nerves	PR play an important role in remyelination after sciatic nerve injury and in myelination in co-cultures of neurons and Schwann cells.		Koenig et al. (1995) and Chan et al. (1998, 2000)
	P0 expression is increased by progesterone and 5α-DHP.	PMP22 expression is increased by allopregnanolone (*in vitro* and *in vivo*).	Melcangi et al. (1999, 2003, 2005)
Neuroprotection in the adult central nervous system	Increased sensitivity to ischemic damage of brain of PR knockout mice. Progesterone treatment fails to provide neuroprotection after MCAO in PR knockout mice. Nestorone provides neuroprotection.	Allopregnanolone treatment protects the brain of PR knockout mice against ischemic damage.	Liu et al. (2012)
	Progesterone does not protect neurons in organotypic spinal cord slice cultures of PR knockout mice.	Allopregnanolone protects neurons in spinal cord slice cultures of PR knockout mice (involvement of $GABA_A$ receptors).	Labombarda et al. (2013)
		Increased synthesis of allopregnanolone in the hippocampus protects neurons against excitotoxic injury and toxins.	Ciriza et al. (2004) and Ishihara et al. (2013)
		Allopregnanolone treatment protects the rat brain against traumatic injury (TBI) or ischemic damage (MCAO).	Djebaili et al. (2004), Sayeed et al. (2006, 2009) and Ishrat et al. (2010)
		Allopregnanolone provides neuroprotection and promotes repair processes (neurogenesis and cognitive improvement) in mice during normal aging and in transgenic models of Alzheimer's disease.	Chen et al. (2011), Singh et al. (2012) and Brinton (2013)

5α-DHP: 5α-dihydroprogesterone; MCAO: middle cerebral artery occlusion, an experimental stroke model; OPC: oligodendrocyte progenitor cells; P0: peripheral myelin protein zero; PMP22: peripheral myelin protein-22; PR: classical intracellular progesterone receptors; PR-A and PR-B: the PR isoforms transcribed from a single gene; PR knockouts: refers to total PR knockouts; TBI: traumatic brain injury.
Nestorone and promegestone are selective PR agonists; mifepristone is a PR (and glucocorticoid) antagonist.

receptors has indeed been documented by a large number of experimental studies. Moreover, the respective significance of PR and allopregnanolone signaling may be dependent on the pathophysiological context, and on many other factors such as the stage of development and species differences. However, future studies on the effects of progesterone on the nervous system should no longer ignore the important role played by the classical intracellular PR. Major recent advances in our understanding of the complex signaling mechanisms of progesterone and allopregnanolone offer new challenging perspectives for our fundamental understanding of the effects of progestogens on the nervous system and for their therapeutic use.

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