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Progesterone: Therapeutic opportunities for neuroprotection and myelin repair

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Abstract

Progesterone and its metabolites promote the viability of neurons in the brain and spinal cord. Their neuroprotective effects have been documented in different lesion models, including traumatic brain injury (TBI), experimentally induced ischemia, spinal cord lesions and a genetic model of motoneuron disease. Progesterone plays an important role in developmental myelination and in myelin repair, and the aging nervous system appears to remain sensitive to some of progesterone's beneficial effects. Thus, the hormone may promote neuroregeneration by several different actions by reducing inflammation, swelling and apoptosis, thereby increasing the survival of neurons, and by promoting the formation of new myelin sheaths. Recognition of the important pleiotropic effects of progesterone opens novel perspectives for the treatment of brain lesions and diseases of the nervous system. Over the last decade, there have been a growing number of studies showing that exogenous administration of progesterone or some of its metabolites can be successfully used to treat traumatic brain and spinal cord injury, as well as ischemic stroke. Progesterone can also be synthesized by neurons and by glial cells within the nervous system. This finding opens the way for a promising therapeutic strategy, the use of pharmacological agents, such as ligands of the translocator protein (18 kDa) (TSPO; the former peripheral benzodiazepine receptor or PBR), to locally increase the synthesis of steroids with neuroprotective and neuroregenerative properties. A concept is emerging that progesterone may exert different actions and use different signaling mechanisms in normal and injured neural tissue.

Keywords: Progesterone; Allopregnanolone; Neuroprotection; Regeneration; Myelin; Traumatic brain injury; Motoneuron; Spinal cord

Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-DHP, 5α-dihydroprogesterone; 5α-DHT, 5α-dihydrotestosterone; ACTH, adrenocorticotropic hormone; AR, androgen receptor; BDNF, brain-derived neurotrophic factor; CBP, CREB Binding Protein; ChAT, choline acetyltransferase; CNS, central nervous system; ER, estrogen receptor; GABA, γ-aminobutyric acid; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HRT, hormone replacement therapy; KO, knockout; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MDN, mediodorsal thalamic nucleus; MPA, medroxyprogesterone acetate; mPR, membrane progesterone receptor; MR, mineralocorticoid receptor; NBM, nucleus basalis magnocellularis; NMDA, *N*-methyl-D-aspartate; PAIRBP1, plasminogen activator inhibitor RNA binding protein-1; PBR, peripheral benzodiazepine receptor; PGRMC1, progesterone membrane receptor component 1; PNS, peripheral nervous system; PR, progesterone receptor; SERM, selective estrogen receptor modulator; SPRM, selective progesterone receptor modulator; SRC, steroid receptor coactivator; TBI, traumatic brain injury; TSPO, translocator protein (18 kDa) (formerly PBR).

Contents

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1. Introduction

The conventional view that the gonadal steroids have only reproductive functions and that adrenal steroids only regulate fluid homeostasis, metabolic pathways and adaptive responses to stress, has completely changed over the past few years. A large number of experimental studies, most performed in rodents, have demonstrated the multiple actions of progestagens, estrogens, androgens, glucocorticoids and mineralocorticoids throughout the nervous system, and their considerable influence on the functioning of neurons and glial cells. Their neurotrophic and neuroprotective effects have attracted much attention because of their therapeutic promise. What makes steroids particularly attractive molecules for treating lesions and diseases of the nervous system is their ability to easily cross the blood–brain and blood–nerve barriers and to very rapidly diffuse throughout the nervous tissues.

Studies on the nonreproductive functions of progesterone and its metabolites in the nervous system have mainly focused on the modulation of neurotransmission. That is, progesterone has been shown to directly influence the activity of a series of neurotransmitter receptors, including the nicotinic acetylcholine receptor (nAChR) and sigma-1 (σ1) receptors (Valera et al., 1992; Léna & Changeux, 1993; Bastianetto et al., 1999; Monnet & Maurice, 2006). Most studied have been the potent positive modulation of γ-aminobutyric acid type A ($GABA_A$) receptors by physiological concentrations of allopregnanolone, the 3α,5α-reduced metabolite of progesterone (3α,5α-tetrahydroprogesterone; Majewska et al., 1986; Belelli et al., 2002). The modulation of $GABA_A$ receptors explains the anaesthetic, analgesic and anxiolytic effects of progestagens and their role in stress, depression, memory, seizure susceptibility and alcohol dependence (Rupprecht & Holsboer, 1999; Morrow et al., 2001).

Compared to research on progesterone's neuromodulatory and psychopharmacological actions, its neuroprotective and neurotrophic effects have been relatively neglected but this situation is beginning to change. Among recent findings, the modulation of $GABA_A$ receptor activity by allopregnanolone has been shown to be involved in the neuroprotective effects of progesterone (Ciriza et al., 2004a; He et al., 2004; Djebaili et al., 2005; Sayeed et al., 2006). Most importantly, it has been shown that progesterone and its metabolites not only promote the viability and regeneration of neurons but also act on the myelinating glial cell oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) and play an important role in the formation of myelin sheaths (Magnaghi et al., 2001; Schumacher et al., 2001; Ghoumari et al., 2003).

Recognition of the neuroprotective potential of progesterone has recently led to the completion of a clinical trial in Atlanta, Georgia. Named "ProTECT" (progesterone for traumatic brain injury (TBI), experimental clinical treatment), this trial tested the usefulness of progesterone as treatment for moderate to severe TBI and included 100 trauma patients (Wright et al., 2007). Stable elevated progesterone levels were achieved following TBI by the intravenous infusion of the natural hormone for 3 days (Wright et al., 2005). The treated patients had more than a 50% lower mortality rate at 30 days post-injury than controls (receiving state-of-the-art treatment but no progesterone). The patients in the moderate TBI group given progesterone tended to have better functional outcomes, although progesterone had no effect on the disability of severe TBI survivors at the 30-day time point. Most importantly, no adverse events could be attributed to prolonged infusion of high doses of progesterone in this trial.

Another clinical trial launched in 2005 is of interest here. Named "POPART'MUS" (prevention of post-partum relapses with progestin and estradiol in multiple sclerosis"), it is a placebo-controlled clinical trial aimed to prevent multiple sclerosis relapses related to the post-partum condition using a synthetic progestin (nomegestrol acetate) in combination with estradiol. Treatment is given immediately after delivery and continuously

during the first 3 months post-partum (el-Etr et al., 2005). A recent prospective study reported a significant decline in the rate of relapses during the third trimester of pregnancy and a significant increase during the first 3 months post-partum compared with the relapse rate observed during the year prior to pregnancy (Confavreux et al., 1998). Thus, relapses decrease when levels of many hormones are elevated, and in particular those of progesterone, and increase when hormone levels decline to pre-pregnancy levels following delivery. Although this trial does not distinguish between the effects of progestin and estrogen (their effects may involve the modulation of immune responses), the demonstration of the promyelinating and neuroprotective effects of progesterone have substantially contributed to the design of the study (el-Etr et al., 2005). Thus, the idea that progestagens may have beneficial influences on neurons and myelin is slowly beginning to make its way into clinical practice.

This recent rise in interest in the therapeutic promise of progesterone for the injured and diseased nervous system contrasts with the poor reputation progestagens have recently acquired in hormone replacement therapies (HRT). In postmenopausal women with an intact uterus, a progestagen is generally administered to prevent estrogen-dependent uterine hyperplasia and malignancy. However, because of the many risks attributed to progestagens, there is an ongoing debate over the safety of their use in HRT (Naftolin & Silver, 2002). An increase in the risks of breast cancer, vascular complications and cognitive decline have been attributed to the use of progestagens (Rossouw et al., 2002; Banks et al., 2003; Thomas et al., 2003; Campagnoli et al., 2005). There are several possible explanations for the apparent detrimental effects following the use of progestagens in HRT but obviously one of the major problems is that they are widely considered a single class of molecules. This misperception is clearly not appropriate and has caused much confusion, because not all progestagens have the same pharmacological and biological properties. Worse, the term progesterone, which should only designate the natural hormone, is frequently used as a generic without any distinction among the different types of natural and synthetic progestagens.

It is necessary to clarify the nomenclature here. The term progestagen, also sometimes wrongly spelled as "progestogen", is a functional definition and refers to natural or synthetic steroids which possess progestational activity. This includes natural progesterone and the synthetic molecules but we propose to extend the definition to include important and biologically active metabolites of progesterone, such as allopregnanolone (3α,5α-tetrahydroprogesterone), even though their effects do not involve the classical intracellular progesterone receptors (PR). The term progestin, as used herein, designates the synthetic progestagens. It is important to stress again the fact that these compounds are very different and do not behave the same. Progestins can include, for example, testosterone derivatives (19-nortestosterone derivatives) and progesterone derivatives (17α-hydroxyprogesterone derivatives and 19-norprogesterone derivatives). The 19-norprogesterone derivatives such as 19-norprogesterone promegestone (R5020) and nomegestrol acetate (the progestin used in the POPART'MUS trial) are among the most selective agonists of the PR (Schindler et al., 2003; Sitruk-Ware, 2004a, 2004b). In contrast, 17α-hydroxyprogesterone derivatives, such as medroxyprogesterone acetate (MPA), the most commonly prescribed contraceptive and replacement progestin in the United States, also binds to the androgen receptor (AR) and to the glucocorticoid receptor (GR; Bamberger et al., 1999). MPA's side effects have largely contributed to the concerns directed against progestagens and even against natural progesterone. In the nervous system, MPA has been shown to antagonize the neuroprotective and promnesic effects of estrogen, and at the molecular level, to block the estrogen-induced expression of the anti-apoptotic protein Bcl-2 (Nilsen & Brinton, 2002; Nilsen & Brinton, 2003). Even on its own, MPA can exacerbate the excitotoxic death of neurons (Nilsen et al., 2006). *In vivo*, MPA has recently been reported to diminish the ability of estrogens to reduce stroke damage in subcortical regions of the rat brain (Littleton-Kearney et al., 2005). The progestin has also been shown to directly inhibit the activity of steroidogenic enzymes, in particular of the human type II 3β-hydroxysteroid dehydrogenase (3β-HSD), an enzyme which converts pregnenolone to progesterone, thus interfering with the biosynthetic pathways of neuroactive progestagens (Lee et al., 1999).

It is important to note that even those progestins, which selectively activate transcriptional responses of the PR, such as the 19-norprogesterone derivatives, do not necessarily mimic all the effects of natural progesterone, in particular within the nervous system. First, they do not metabolize to the neuroactive metabolite allopregnanolone and they may be inactive at the level of neurotransmitter receptors such as $GABA_A$ receptors (Fig. 1). Second, as will be discussed below, the actions of progesterone in the brain involve multiple signaling mechanisms, some of which do not involve the classical PR but rather novel membrane receptors. These novel receptors may show particular pharmacological profiles, and their affinity for synthetic molecules needs to be verified.

The aim of this review is to discuss the actions of natural progesterone in both the CNS and PNS, with particular emphasis on its neuroprotective effects and its role in myelination. Our current knowledge about progesterone's multiple mechanisms of action in the nervous system will be detailed, as they offer novel perspectives for the development of more safe and selective progestins. Attention will be drawn to the local synthesis and metabolism of progesterone within the nervous system. Indeed, progesterone is produced not only by the steroidogenic endocrine glands (ovaries, placenta and adrenal glands) but also by neurons and glial cells. There is now strong evidence that an increase in the local synthesis of progesterone may be part of the mechanisms by which nerve cells cope with neurodegeneration. As a consequence, its stimulation offers very promising possibilities for providing protection and promoting regeneration in the nervous system.

2. Steroids in neuroprotection and neuroregeneration

Before going into the neuroprotective and promyelinating actions of progesterone, it is worthwhile to situate them in relation to the nonreproductive functions of the other major steroid hormones in

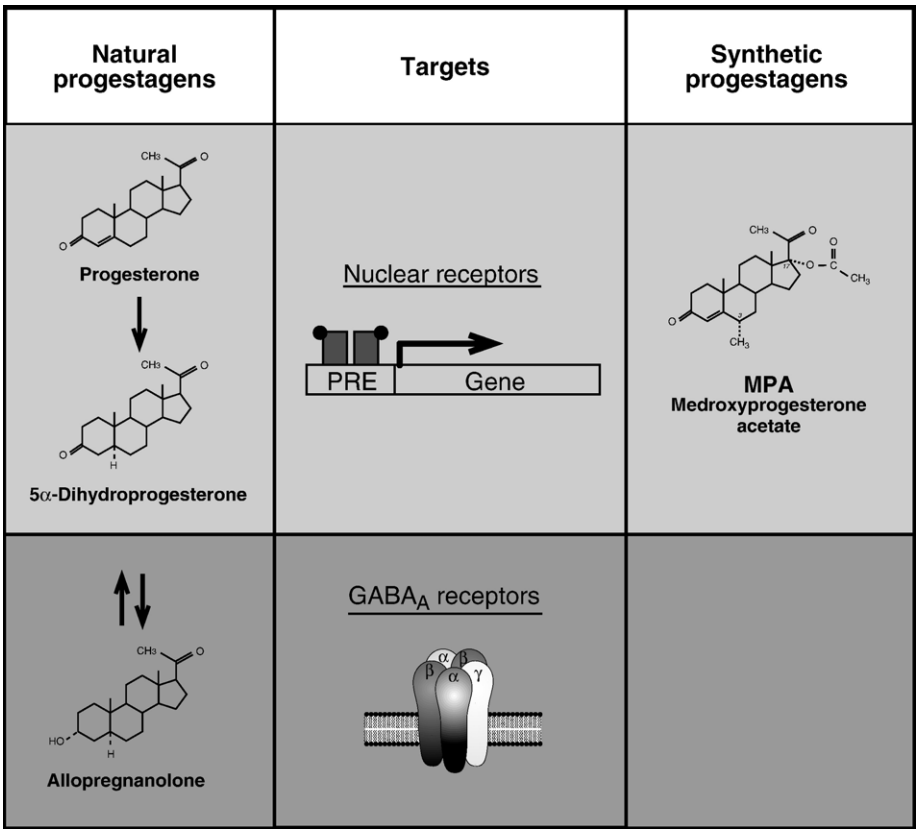

Fig. 1. Actions of progesterone and of synthetic progestins. Progesterone is unidirectionally converted by steroid 5α-reductases to 5α-dihydroprogesterone (5α-DHP). Two 5α-reductase isozymes are encoded by distinct genes. The type 1 isoform is expressed throughout the rat brain at all stages of development, whereas the type 2 isoform shows a more restricted distribution (Melcangi et al., 1998b; Patte-Mensah et al., 2004). Both progesterone and 5α-DHP bind to the intracellular PR, which activate gene transcription by interacting as homodimers with progesterone response elements (PRE) of target genes. The conversion of 5α-DHP to allopregnanolone is catalyzed by cytosolic NADP-dependent aldo-keto reductases (ARK) (Penning et al., 2004). The oxidation of allopregnanolone to 5α-DHP is catalyzed by membrane-bound NAD-dependent short-chain dehydrogenases/reductases (SDR; Belyaeva & Kedishvili, 2006). In contrast to natural progesterone, synthetic progestins, such as MPA are not converted to GABA$_A$ receptor-active allopregnanolone.

the nervous system. Among these, the neurotrophic and neuroprotective effects of the estrogens have attracted most attention, having been extensively studied in a variety of animal and in vitro models of neural injury and degeneration. Interestingly, males as well as females are sensitive to the protective effects of estrogen, as estradiol has been shown to prevent ischemia-induced learning disability and neuronal loss in both sexes (Sudo et al., 1997; Wise et al., 2000).

Reduced levels of estradiol have been shown to compromise the functioning and survival of neurons and to result in alterations in memory processes (McEwen, 1999a; Garcia-Segura et al., 2001; Lee & McEwen, 2001; Behl, 2002; Wise, 2002). Estradiol present in the brain is derived from both the circulation and from local synthesis. In the brain, the estrogen-synthesizing enzyme aromatase plays a very important role in neuroprotection. Thus, after pharmacological inhibition of the enzyme or in aromatase-deficient mice, vulnerable brain structures, such as the hippocampus, become much more susceptible to neurodegeneration after excitotoxic injury (Garcia-Segura et al., 2003). The crossing of aromatase gene knockout (KO) mice with a mouse model of Alzheimer's disease (APP23 transgenic mice) demonstrated that estrogen depletion in the brain leads to early onset and increased β-amyloid peptide deposition, suggesting an increased risk for developing neurodegenerative pathology (Yue et al., 2005).

The therapeutic promise of estrogens for treating lesions and degenerative diseases of the nervous system has spurred the development of synthetic estrogen-like compounds with more selective neuroprotective activities either reduced binding to the classical intracellular estrogen receptors (ER) or selective binding to 1 of 2 ER isoforms (ERα or ERβ) (Green et al., 2001; Brinton, 2004; Simpkins et al., 2004; Manthey & Behl, 2006). There is indeed some concern with possible side effects of estradiol and conventional synthetic estrogens, such as increased risk of breast cancer (Banks et al., 2003; Clarke, 2006). Also, although most experimental studies have reported beneficial effects of estrogens on neurons, they are not universally neuroprotective and may eventually exacerbate brain damage by increasing neuronal excitability (Emerson et al., 1993; Harukuni et al., 2001; Marriott et al., 2002; Smith & Woolley, 2004).

Some of the neuroprotective effects of androgens are mediated by their conversion to estrogens (Veiga et al., 2003). However, androgens also exert neuroprotective and neuroregenerative effects on their own but these have been much less studied (Bialek et al., 2004). Thus, different populations of motoneurons, such as the facial motoneurons of the hamster and the spinal and pudendal motoneurons of the rat, contain androgen AR. Testosterone promotes their survival and regeneration after axotomy, and these

beneficial effects can be mimicked by nonaromatizable androgens and blocked by AR antagonists (Jones et al., 2001). However, estradiol also contributes to the survival and regeneration of the motoneurons after axotomy by independent mechanisms (Huppenbauer et al., 2005). Androgens are also required for maintaining the structural integrity of motoneurons of the rat nucleus of the bulbocavernosus, a group of neurons in the lower lumbar spinal cord innervating the penis (Jordan et al., 2002).

Testosterone and its metabolites 5α-dihydrotestosterone and 3α,5α-androstanediol have also been shown to protect granule neurons of the dentate gyrus from apoptosis in adrenalectomized male and female rats (Frye and McCormick, 2000a,b). Metabolism to 3α,5α-androstanediol may play an important role in some of the neuroprotective effects of testosterone, as it does in the antiseizure effects of the hormone (Frye & Reed, 1998).

The story of the trophic and damaging effects of the glucocorticoids is a more complicated one. They are important regulators of neuronal activity and of inflammatory responses but their effects are very dependent on concentration and time of exposure, requiring a fine and tightly controlled regulation of their actions. Thus, either prolonged reduced or prolonged elevated levels of glucocorticoids may result in neuron death and in harmful immune responses within the brain, a condition which has been summarized as, "Too little is like too much" (McEwen, 1998; De Kloet, 2004; Glezer & Rivest, 2004; Herbert et al., 2006).

The effects of glucocorticoids are mediated by 2 types of receptors: the mineralocorticoid receptor (MR or type 1 receptor), which shows high affinity for both glucocorticoids and mineralocorticoids, and the GR (type 2 receptor), which is selectively activated by elevated levels of glucocorticoids, corticosterone in rats and mice and cortisol in humans. Signaling of low levels of glucocorticoids via the high-affinity MR has been shown to promote neuronal survival within specific brain regions, such as the dentate gyrus of the hippocampus, and also following injury (Vaher et al., 1994; Almeida et al., 2000; Macleod et al., 2003). The consequences of GR activation by elevated levels of glucocorticoids is a more complicated and controversial issue. It may provide an adaptive response to stress and to injury if limited in time but prolonged exposure to elevated levels of glucocorticoids can become damaging for the brain (Sapolsky et al., 2000; McEwen, 2002). This is an important issue when discussing the significance of steroid influences on the injured nervous system because glucocorticoids continue to be used for the chronic treatment of lesions of the head and spinal cord and also because endogenous levels of glucocorticoids are strongly upregulated in response to injury.

Because of the complexity of their actions, it is not surprising that both damaging and beneficial effects of glucocorticoids on the injured nervous system have been reported. Thus, glucocorticoids acting via the GR have been shown to exacerbate neuronal damage in experimental models of traumatic, ischemic and excitotoxic cerebral injury (Antonawich et al., 1999; Kaufer et al., 2004). In a recent clinical study of 10,000 adults with head injury, methylprednisolone treatment was found to increase the risk of death and severe disability (Roberts et al., 2004; Edwards et al., 2005), strongly suggesting that corticosteroids should not be used in the treatment of head injury. However, there is also experimental evidence for beneficial effects of glucocorticoids after spinal cord injury, where high doses of glucocorticoids have been shown to stimulate expression of the Na^+, K^+-ATPase and growth factors, to protect against glutamate toxicity and promote axonal regeneration (Ogata et al., 1993; De Nicola et al., 1998; Nash et al., 2002). High-dose methylprednisolone continues to be the standard of care after spinal cord injury for many neurosurgeons, but its use is growing more controversial, as some clinicians believe that the risks may outweigh its modest neurological benefits (Hall, 2003).

This outline shows that the major groups of steroid hormones exert pleiotropic effects in the nervous system and influence the viability and regenerative capacity of neurons. It is within this context that the neurotrophic, neuroprotective and promyelinating effects of progestagens must be understood. It is unlikely that the different steroids act independently, and they may have either similar, complementary, redundant or opposing actions. Unfortunately, laboratories are often specialized in studying one particular class of steroids, and few studies have addressed the important question of progestagens' interactions. For example, some of the neuroprotective actions of progesterone resemble those of estradiol, such as the increase in the expression of antiapoptotic genes and the down-regulation of proapoptotic ones (Garcia-Segura et al., 1998; Nilsen & Brinton, 2002; Yao et al., 2005). Conversely, estrogens and progestagens exert opposing effects on neuronal excitability, while estrogens increase the excitability of neurons, progesterone and its reduced metabolites in general reduce their activity, an effect which may be neuroprotective (Smith & Woolley, 2004).

In some regions of the nervous system, the genomic actions of progesterone are dependent on estrogen priming. For example, it has recently been recognized that 2 distinct PR systems exist in the brain: receptors localized in the hypothalamus and in some limbic structures are induced by estradiol, whereas PR expression in cerebral cortex, septum, caudate putamen, midbrain and cerebellum is unaffected by estrogenic stimulation (MacLusky & McEwen, 1978, 1980a, 1980b; Parsons et al., 1982; Romano et al., 1989). The PR gene of different species has been demonstrated to contain estrogen-responsive elements (ERE) but why the regulation of its expression by estradiol is restricted to certain tissue compartments is unknown (Savouret et al., 1989; Kastner et al., 1990; Kraus et al., 1993, 1994). Most importantly, the PR is down-regulated by progesterone treatment precisely in those brain regions where its expression is regulated by estradiol. In contrast, in brain regions, such as the cerebral cortex, progesterone treatment does not affect PR content (Camacho-Arroyo et al., 1994; Guerra-Araiza et al., 2003). Similarly, available data suggest that PR expression may not be influenced by estradiol and progesterone in the spinal cord and in peripheral nerves (Jung-Testas et al., 1996; Labombarda et al., 2000, 2003). Thus, it is very likely that in those compartments of the nervous system, PR-dependent actions of progesterone may not be influenced by estrogen status and may not decrease as a consequence of prolonged exposure to this hormone. However, this fact by no means excludes the possibility of reciprocal

interactions between the complex signaling networks of progesterone and estradiol.

Other steroid interactions in the nervous system, which need to be explored, are those between progestagens and glucocorticoids. At the molecular level, there are examples of a complex cross-talk between both types of hormones but their physiological meaning within the nervous system has not been studied. For example, it is well known that progesterone cross-binds with the GR in breast cancer cells and adipocytes (Pedersen et al., 1992). In the latter, progesterone acts as an antiglucocorticoid and inhibits glucocorticoid-dependent aromatase induction (Schmidt et al., 1998; Pedersen et al., 2003). In other tissues, progesterone has been shown to mimic the effects of glucocorticoids by binding to the GR (Sugino et al., 1997; Telleria et al., 1998). Glucocorticoids, on the other hand, have been found to cross-bind to the PR and to mimic some of the effects of progesterone (Leo et al., 2004). An expression profiling of glucocorticoid- and progesterone-regulated genes in human breast cancer cells has revealed that the 2 types of hormones regulate both overlapping and distinct sets of genes. Interestingly, the number of differentially regulated genes was almost the same as that regulated by each of the hormones individually (Wan & Nordeen, 2002). Some studies suggest that nuclear coactivator and corepressor proteins may play a significant role in determining distinct and similar transcriptional effects of the PR and GR, and this within specific promoter- and cell-dependent contexts (Song et al., 2001; Li & O'Malley, 2003).

In light of the potential interactions between PR and GR signaling, it is intriguing that some of the effects of glucocorticoids in the spinal cord resemble those of progesterone, whereas others are distinctly different. For example, in the injured rat spinal cord, both progesterone and glucocorticoids have been shown to increase expression of the α3 and β1 subunits of the Na^+, K^+-ATPase, an effect which may afford neuroprotection (Gonzalez et al., 1994; De Nicola et al., 1998; Labombarda et al., 2002). However, in the spinal cord of Wobbler mice, progesterone and glucocorticoids had different effects on the expression of the growth-associated protein GAP-43: progesterone up-regulated but corticosterone down-regulated its expression (Gonzalez Deniselle et al., 1999, 2001). This mouse, which will be described in more detail below, is characterized by severe motoneuron degeneration and astrogliosis in the spinal cord and is a particularly useful model for the study of motoneuron diseases, including amyotropic lateral sclerosis (ALS). The expression of brain-derived neurotrophic factor (BDNF) in the CNS is also differentially regulated by progesterone and glucocorticoids: up-regulated by the former and down-regulated by the latter (Chao & McEwen, 1994; Gonzalez et al., 2004; Hansson et al., 2006).

3. Neuroprotective effects of progesterone

The neuroprotective effects of progesterone have been demonstrated after experimental lesion of the rodent brain and spinal cord. A much studied model of TBI uses a bilateral contusion lesion of the rat medial prefrontal cortex, which produces cognitive deficits typically observed after human frontal lobe injury (Hoffman et al., 1994; Stein, 2001). It results in edema, secondary excitotoxic neuronal death in the vicinity of the lesion, and subsequent retrograde neuronal degeneration in both the mediodorsal thalamic nucleus (MDN) and the nucleus basalis magnocellularis (NBM; He et al., 2004). Progesterone treatment reduced both edema and secondary neuronal losses and improved behavioral recovery after TBI in male and female rats. Available experimental data show that prolonged administration of the hormone leads to more complete behavioral recovery after TBI (Galani et al., 2001; Cutler et al., 2006a). Interestingly, females are protected against edema and neuron death by their high endogenous levels of progesterone, an effect which becomes particularly apparent after the induction of pseudopregnancy (Roof et al., 1993, 1994). Pretreating ovariectomized female rats with low physiological concentrations of progesterone also reduced hippocampal neuron loss in response to TBI (Robertson et al., 2006).

Progesterone has also been shown to protect neurons, which are particularly sensitive to injury, such as the pyramidal neurons of the hippocampus, against experimentally induced cerebral ischemia in cats (Gonzalez-Vidal et al., 1998; Cervantes et al., 2002). In rats, progesterone given prior to middle cerebral artery occlusion (MCAO) decreased the infarct size and neurological deficits (Jiang et al., 1996; Kumon et al., 2000). A recent study on functional outcomes after MCAO in male mice showed a beneficial effect of progesterone on motor ability and spatial memory performance evaluated on the rotarod and in the Morris water maze, respectively (Gibson & Murphy, 2004).

In the rat brain, neuroprotective effects of progesterone have also been demonstrated for midbrain dopaminergic neurons. Both progesterone and estradiol were found to protect dopaminergic neurons against degeneration induced by 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), a finding which would be consistent with a hormonal influence on the deterioration of dopaminergic functions with age and on the development of Parkinson's disease (Callier et al., 2001). There is a higher incidence of Parkinson's disease in men compared with women and the risk of its occurrence is increased in women after the onset of menopause (Ragonese et al., 2004).

Marked neuroprotective effects of progesterone have been demonstrated in the spinal cord. For example, chronic treatment with progesterone for 5 days after contusion injury in the spinal cord of male rats reduced the size of the lesion and prevented secondary neuronal loss (Thomas et al., 1999). Progesterone is also an important neuroprotective factor for spinal motoneurons. This has been demonstrated after spinal cord transection and in the Wobbler mouse (De Nicola et al., 2003; Gonzalez Deniselle et al., 2005; De Nicola et al., 2006). After complete transection of the spinal cord, progesterone treatment preserved the Nissl bodies of the ventral horn motoneurons, restored choline acetyltranferase (ChAT) levels, normalized the expression of the Na^+, K^+-ATPase and increased GAP-43 and BDNF message and protein (Labombarda et al., 2002; Gonzalez et al., 2004). As already mentioned, the Wobbler mouse is a particularly useful model for the study of motoneuron diseases.

The first manifestations of the disease are already observed at 2–3 weeks of age (Duchen & Strich, 1968; Price et al., 1994). At 2 months old, symptomatic Wobbler mice presenting severe clinical signs including tremor, ambulatory difficulty and diminished muscle strength were subcutaneously implanted with progesterone pellets for only 2 weeks, the neuropathological changes of spinal motoneurons were less severe, motoneuron vacuolation was reduced and there was better preservation of the endoplasmic reticulum and of the mitochondria. Remarkably, progesterone treatment also had beneficial effects on muscle strength of the animals (Gonzalez Deniselle et al., 2001, 2002a, 2002b).

In light of the recent discovery that a missense mutation in the gene encoding the vacuolar–vesicular protein sorting factor Vps54 is responsible for the Wobbler phenotype (Schmitt-John et al., 2005), it was a significant finding that retrograde axonal transport is impaired in Wobbler motoneurons, as shown by the injection of fluorogold into the limb muscles and its retrograde tracing. Most importantly, transport could be restored by treating the animals for 8 weeks with progesterone, as was forelimb muscle strength (Gonzalez Deniselle et al., 2005). The demonstration of a role for progesterone in regulating axonal transport also has important implications for the treatment of other neurodegenerative diseases and age-dependent alterations of nervous functions. Reduced axonal transport has been proposed to play an early and causative role in the development of Alzheimer's disease (Stokin et al., 2005), so it is possible that progesterone treatments could prove beneficial in delaying onset of this disorder. In a model of diabetic neuropathy, induced in rats by an injection of streptozotocin, prolonged treatment with progesterone or its reduced metabolites had beneficial effects on peripheral nerves at the neurophysiological, functional and neuropathological levels (Leonelli et al., 2007).

The mechanisms by which progesterone promotes morphological and functional recovery after injury of the nervous system are not well understood, and they appear to involve multiple actions (progesterone signaling at the cellular level will be discussed in Section 6). An important consequence of progesterone treatment after TBI is the reduction of lipid peroxidation, but the underlying mechanisms still need to be specified (Roof et al., 1997). The peroxidation of lipids is a complex phenomenon, involving distinct enzymatic pathways as well as nonenzymatic mechanisms, such as free radical-mediated peroxidation, and it is reduced by the actions of different antioxidant enzymes (Niki et al., 2005). An increase in the concentration of lipid peroxidation products within the brain is also observed during the aging process (Pratico & Sung, 2004). In addition, the oxidation of neuronal lipids resulting from an oxidative imbalance has been proposed to play a significant role in Alzheimer's pathogenesis (Pratico & Sung, 2004), and consequently, as noted above, may represent an interesting therapeutic target for progesterone in the early stages of the disease. The increased exposure of aging tissues to oxidative stress partly results from decreased activity of antioxidant enzymes, such as the superoxide dismutases (SOD). The prolonged treatment of middle-aged and old acyclic female rats (12, 18 and 24 months) with low doses of progesterone, estradiol or a combination of both steroids increased SOD activity and reduced lipid peroxidation (Moorthy et al., 2005a, 2005b). The age-dependent accumulation of oxidative damage is also a consequence of a decline in mitochondrial function, another major component of both the normal aging process and neurodegeneration (Harman, 1972; Kokoszka et al., 2001; Brand et al., 2004; Loeb et al., 2005; Schriner et al., 2005). Many of the reactive oxygen species (ROS) involved in oxidative stress are a toxic by-product of the mitochondrial energy production pathway.

Recently, much attention has focused on the role of mitochondria in neurodegeneration (Melov, 2004; Beal, 2005; Toescu, 2005), and this cellular organelle is another important target for the actions of progesterone and estradiol. One of the prevalent neuropathological changes found in spinal motoneurons of Wobbler mice are damaged mitochondria with severe vacuolation. Treatment with progesterone resulted in the restoration of a normal appearance of the mitochondria (De Nicola et al., 2003). In addition, both progesterone and estradiol have been shown to protect neurons against apoptotic cell death by increasing the expression of antiapoptotic proteins residing in the outer mitochondrial membrane, such as Bcl-2, and by down-regulating proapoptotic gene expression (bax and bad) and the caspase-3 enzyme (Garcia-Segura et al., 1998; Alkayed et al., 2001; Nilsen & Brinton, 2002; Djebaili et al., 2005; Yao et al., 2005; Wise, 2006). The expression of Bcl-2 family proteins is regulated by nuclear steroid actions, and the newly synthesized proteins are translocated to the outer mitochondrial membrane (Schlesinger & Saito, 2006). However, steroids can also exert direct actions on mitochondria, as has been demonstrated for estrogens and glucocorticoids (Chen et al., 2005; Stirone et al., 2005; Duckles et al., 2006; Pedram et al., 2006; Psarra et al., 2006). In the low physiological range, progesterone has been shown completely to reverse postinjury alterations in mitochondrial respiration (Robertson et al., 2006). Whether and to what extent progesterone directly and differentially acts on the mitochondria still needs to be clarified.

Progesterone exerts many other actions which can be related to its neuroprotective effects. For example, progesterone regulates the expression of aquaporin 4 (AQP4), a membrane-channel protein involved in water homeostasis, in the injured brain. Aquaporins are distributed throughout the brain and may play a significant role during edema formation (Guo et al., 2006). As we mentioned earlier, some of the actions of progesterone resemble those of the estrogens. Like estradiol, progesterone reduces inflammation by repressing the activation of microglial cells and by inhibiting the production of pro-inflammatory cytokines (Miller & Hunt, 1998; Drew & Chavis, 2000; He et al., 2004; Pettus et al., 2005) and upregulates the expression of neurotrophins, such as BDNF (Gonzalez et al., 2004, 2005; Scharfman & MacLusky, 2005). It also protects neurons against glucose deprivation and the toxicity of glutamate, $FeSO_4$ and β-amyloid peptides (Ogata et al., 1993; Goodman et al., 1996; Nilsen & Brinton, 2002).

4. The role of progesterone in myelin formation

A particular asset of progesterone is that it not only provides strong neuroprotection but also promotes myelin formation,

either during development or during the remyelination of axons in the adult. This was first demonstrated in the regenerating male mouse sciatic nerve after a cryolesion and in explant cultures of rat dorsal root ganglia (DRG) isolated from embryonic rats and mainly composed of sensory neurons and Schwann cells, after antimitotic treatment (Koenig et al., 1995). In a later study, progesterone was found to accelerate the formation of myelin sheaths in co-cultures of neurons and Schwann cells (Chan et al., 1998). Whether progesterone promotes myelination of peripheral nerves by acting directly on Schwann cells or indirectly by acting on neurons still needs to be clarified. Whole-cell radioligand binding assays suggest the presence of specific and saturable progesterone binding sites in Schwann cells (Jung-Testas et al., 1996), and the PR has been detected by immunocytochemistry in Schwann cells grown either in culture or within the rat sciatic nerve (Magnaghi et al., 2001). In contrast, another study has reported that in cocultures of DRG neurons and Schwann cells, PR mRNA and protein were present only in neurons, not in Schwann cells (Chan et al., 2000). Moreover, in a recent study, purified rat Schwann cells and various Schwann cell lines were found to express only extremely low amounts of PR, not sufficient to activate the transcription of a progesterone-sensitive reporter gene (Groyer et al., 2006).

Progesterone also promotes myelination by oligodendrocytes in the CNS, as first demonstrated in explant cultures of cerebellar slices taken from 7-day-old rats and mice (Ghoumari et al., 2003). In these organotypic cultures, myelination is very intense during the second postnatal week, precisely at a time when endogenous levels of progesterone are elevated in the cerebellum (Notterpek et al., 1993; Ukena et al., 1999). A stimulatory effect of progesterone on myelination was observed in cerebellar slices of both sexes and involved the classical PR but not observed in cerebellar slice cultures from 7-day-old PR KO mice (Ghoumari et al., 2003). Progesterone was then shown to stimulate the proliferation and maturation of oligodendrocyte progenitor cells in these slices (Ghoumari et al., 2005). An earlier study had already shown that adding progesterone to cultures of glial cells isolated from neonatal rat brains increased the number of oligodendrocytes (Jung-Testas et al., 1989). More recently, the addition of progesterone to the medium of cultured oligodendrocytes increased their branching (Marin-Husstege et al., 2004).

Progesterone administration was also found to promote remyelination by oligodendrocytes after a toxin-induced demyelination in the cerebellar peduncle of 9-month-old male rats (Ibanez et al., 2004). This was a particularly significant finding because at this age the capacity to regenerate myelin sheaths is already much reduced in male rats (Gilson & Blakemore, 1993; Shields et al., 1999; Hinks & Franklin, 2000; Sim et al., 2002). Interestingly, the extent of oligodendrocyte remyelination was significantly less in the middle-aged males compared with females, pointing to a sex-associated divergence in remyelination efficiency with age (Li et al., 2006). This observation is particularly intriguing in the light of the clinical observation that both age and gender are determining factors in reaching disability milestones in multiple sclerosis (Confavreux & Vukusic, 2006a, 2006b).

Another important finding was that 3 days after spinal cord transection, expression of myelin basic protein (MBP) at the mRNA and protein levels was restored to control levels by progesterone treatment (Labombarda et al., 2006a). This short-term effect of the hormone treatment most likely reflected the protection of oligodendrocytes, as new myelin sheaths are not formed in such a short time. However, the observation that progesterone treatment also increased the density of $NG2^+$ oligodendrocyte progenitors strongly suggests that myelin repair processes were initiated or enhanced (Labombarda et al., 2006a). These effects of progesterone may be particularly relevant to the protection and regeneration of the spinal cord after injury, where the demyelination of spared axons contributes to secondary neuronal degeneration, the extension of the lesion and subsequent functional deterioration (Faulkner & Keirstead, 2005).

5. Progesterone: an efficient and safe hormone

Several observations make progesterone a particularly attractive trophic agent for the injured brain, spinal cord and peripheral nerves: (1) progesterone has a surprisingly large therapeutic window; (2) even during aging, the nervous system appears to remain sensitive to the beneficial effects of progesterone; (3) the hormone is neuroprotective in both males and females; (4) there are very few reports of negative effects of progesterone on the nervous system; and (5) there may be no harmful effects of progesterone in the peripheral target tissues, including the breast and the cardiovascular system.

5.1. A large therapeutic window for progesterone

Even when administered as late as 2 hr after the onset of MCAO, progesterone still provided therapeutic benefit (Chen et al., 1999). More significant, progesterone was still effective in reducing edema and in protecting neurons after TBI in rats when treatment was delayed as much as 24 hr (Roof et al., 1996). In the ProTECT trial described above, progesterone administration was delayed for 6–7 hr in order to obtain proxy consent required to begin the treatment (Wright et al., 2007).

5.2. Sensitivity of the aging nervous system to progesterone

Whether there is an age limit for the beneficial effects of progesterone on the nervous system is an important question when considering its therapeutic use. There is now strong experimental evidence that the aging nervous system remains sensitive to progesterone, and that its administration even reverses some age-dependent structural abnormalities. As already mentioned, the capacity to repair myelin in the brain decreases with age but treatment with progesterone promotes the remyelination of axons in middle-aged male rats (Ibanez et al., 2003b, 2004). Treatment of very old male rats (22–24 months) for 1 month with progesterone or its reduced metabolites allowed a reversal not only of the age-dependent decline in peripheral myelin protein expression but also of age-related structural abnormalities of the peripheral myelin sheaths. These

effects were specific for progesterone and its metabolites, as they could not be mimicked by the administration of androgens (Melcangi et al., 1998a; Azcoitia et al., 2003).

Middle-aged female rats remain responsive to the protective actions of progesterone, and the administration of either progesterone or estradiol alleviated cerebral stroke in these animals (Alkayed et al., 2000). In another study, the pretreatment of reproductively senescent female rats (14–18 months) with estradiol alone or combined estradiol and progesterone also reduced cortical infarct volume after MCAO (Toung et al., 2004).

Both middle-aged (between 9 and 12 months) and old (between 18 and 24 months) subjects continue to respond to the anxiolytic effects of progesterone (Frye et al., 2006a). The anxiety-reducing effects of progesterone do not require the intracellular PR, because the effect is seen in young and aged PR KO mice (Reddy et al., 2005). However, anxiolysis does require the conversion of progesterone to the GABA-active metabolite allopregnanolone (Brot et al., 1997; Akwa et al., 1999), and is no longer observed in mice deficient of the type 1 5α-reductase (Frye et al., 2004). That the brain of senescent mice continues to be responsive to progesterone and its metabolites was also demonstrated by another study showing that middle-aged and old female mice primed with estradiol continue to show lordosis behavior after the intraventricular injection of progesterone or allopregnanolone (Frye et al., 2006b). Lordosis is a stereotypic posture adopted by a sexually receptive female rodent in response to a mount by a male.

There is so far little information concerning changes in the brain levels of progesterone with aging. In a recent study, decreased levels of progesterone were measured in the hippocampus and cerebral cortex of aged, senescence-prone male SAMP/8 mice. These age-dependent changes in progesterone correlated with changes in the behavioral efficacy of ligands of the σ1 receptor (Phan et al., 2005; for a discussion of the role of progesterone in modulating σ1 receptor functions, see Section 6.2).

5.3. Progesterone is neuroprotective in males and females

When studying the effects of progesterone on the nervous system, it is important to be alert to the possible contribution of structural and biochemical sex differences (Arnold & Gorski, 1984; McEwen, 1999b; Meador et al., 2004). There is increasing recognition that gender differences may influence the incidence and development of diseases and the responses to therapies (Becker et al., 2005). The effects of steroids may also differ between females and males and data obtained for 1 gender may not necessarily apply to the other.

Sex differences in the sensitivity of the brain to progesterone have been described mainly for reproductive functions, and there are surprisingly few observations of a possible influence of gender on the response of the adult nervous system to the trophic and protective effects of progesterone or estradiol. Thus, treatment with progesterone provides similar neuroprotection in males and in females after TBI. Furthermore, the differential sensitivity of the male and female rodent brain to injury appears to be largely determined by the presence of different levels of progesterone. Thus, the more favorable outcome following cerebral stroke or TBI in female rats compared with males may result mainly from the presence of high endogenous levels of progesterone in the females (Roof et al., 1993; Stein & Hoffman, 2003).

However, a recent study has revealed that the effects of progesterone and its 5α-reduced metabolites on the expression of peripheral myelin protein genes differs between males and females (Magnaghi et al., 2006) and can be taken to suggest that attention must be given to the possible influences of gender on functional outcomes after neurosteroid treatments.

5.4. Few reports of negative effects of progesterone

Attention has already been drawn to the disruptive effects of synthetic progestins, such as MPA on the nervous system (Stein, 2005). However, only a few isolated studies have reported an absence of effect or negative actions of natural progesterone in the injured nervous system. One study did not find a beneficial effect of progesterone after ischemic insult (Toung et al., 2004) and 2 dose–response studies have raised concerns about the possibility that high doses of progesterone (30–60 mg/day) may exacerbate the outcome of MCAO or TBI in rodents (Murphy et al., 2000; Goss et al., 2003). It has also been reported that progesterone may inhibit the neuroprotective effects of estradiol in the rat hippocampus after systemic kainate administration, which induces excitotoxic neuron death (Rosario et al., 2006). However, this result contrasts with other reports demonstrating neuroprotective effects of progesterone and its reduced metabolites in the hippocampus after excitotoxic lesions (Ciriza et al., 2004b, 2006). Likewise, an observation suggesting that progesterone may exacerbate cerebrovascular inflammatory responses (Sunday et al., 2006) contrasts with numerous reports of beneficial effects of progesterone in experimentally induced cerebral ischemia, where inflammation of the cerebral vasculature is a key process.

The influence of progesterone may also be dependent on the type and severity of a brain lesion. Thus, sex differences in the outcome of TBI favoring females, consistently observed after diffuse weight-drop-induced TBI, could not be confirmed after more severe focal impact injury, characterized by a very fast evolution of neurodegeneration (Hall et al., 2005a, 2005b). Another issue of concern is how and when progesterone is administered. In the Murphy et al. paper cited above, high-dose progesterone was given for 3 weeks prior to MCAO occlusion and then abruptly terminated on the day the occlusion was created. In a series of studies, it was shown that abrupt termination of progesterone treatment led to an exacerbated inflammatory cytokine response and worsened functional outcomes (Cutler et al., 2006a, 2006b). Such results may account for some of the negative results cited here. Withdrawal of progesterone has indeed been shown to have profound influences on neuronal functions: it leads to increased seizure susceptibility, insensitivity to benzodiazepines and decreased GABAergic inhibition. These withdrawal properties were attributable to increased expression of the $GABA_A$ receptor α4 subunit (Smith et al., 1998a). The GABA modulatory metabolite allopregnanolone was shown to be the active compound responsible for this withdrawal effect (Smith et al., 1998b).

5.5. Effects of progesterone in peripheral target tissues: signaling and nonneuronal benefits

It is now well recognized that the administration of some synthetic progestins can increase the risk of breast cancer. This is very likely to be a consequence of their nonprogesterone-like effects (Campagnoli et al., 2005). Thus, interactions with the GR and disruption of protective AR signaling may both contribute to the increased breast cancer risk in response to MPA (Ouatas et al., 2003; Buchanan et al., 2005). In contrast to the progestins, elevated levels of endogenous progesterone have been proposed to be protective (Micheli et al., 2004; Kaaks et al., 2005). Moreover, no increase in the risk of breast cancer was observed when estradiol was administered together with micronized progesterone to postmenopausal women (Fournier et al., 2005). Since 1980, oral micronized progesterone has been widely used in Europe, especially France. This is natural progesterone whose average particle size has been reduced, leading to decreased breakdown in the gastrointestinal tract, a longer half-life and enhanced bioavailability. Its use is well tolerated and it is effective for the inhibition of endometrial growth (Miller, 1995; Judd et al., 1996; de Lignieres et al., 2002).

In the late 1980s and early 1990s, some highly controversial clinical studies began to accumulate suggesting that endogenous levels of circulating estrogen and progesterone could affect the outcome of mastectomy in premenopausal patients (Hrushesky et al., 1988; Senie & Tenser, 1997). Thus far, about 18 *prospective* clinical studies have been conducted ranging from as few as 36 patients to over 1600 (Chaudhry et al., 2006). Of these reports, 12 of 18 found that timing of the surgery had no overall effect in predicting morbidity and mortality; however, 5 of the studies reported that outcomes were significantly better when the mastectomies were performed during the luteal phase of the menstrual cycle when progesterone relative to estrogen is higher. These beneficial outcome differences ranged from 71% to 95% better outcomes compared with patients given surgery during the follicular phase when estrogen was higher. The general hypotheses underlying these positive studies was based on the notion that naturally circulating levels of progesterone would attenuate the proliferation of breast cells, both normal and pathological, and increase cohesion between the cells, thus rendering them less likely to metastasize (Navarrete et al., 2005). As noted above, progesterone can also act to reduce the availability of receptors for estrogen, making stimulation of cells by estrogen less likely and perhaps triggering apoptosis instead (Badwe et al., 1991). When endogenous progesterone is low or when estrogen is unopposed, some investigators as early as 1991 proposed that mortality from breast cancer is significantly higher, perhaps because estrogen is thought to stimulate vascular endothelial growth factor, which in turn would enable tumors to grow more readily because of increased blood supply (Wood et al., 2005). Further, other studies have shown that obese women who have a tendency to store estrogen have a higher mortality rate than thin women with the same diagnosis (Badwe et al., 2000). In 2000, Badwe et al. (2000) performed a metaanalysis on 36 studies on over 10,000 women examining the timing of surgery on the outcome of breast cancer. The authors concluded that there was an odds reduction of 15±8% in favor of those who had their surgeries in their luteal phase of the menstrual cycle. On the one hand, to many, the results remain controversial and will probably not be resolved unless a large-scale prospective study (including perhaps administration of progesterone for several days prior to surgery) is performed to settle the issue. On the other hand, it is easy and simple to test for progesterone levels in premenopausal women and it could save their lives, so one can only wonder why surgeons in general may be resistant to performing the surgery during the luteal phase, since at worst the negative studies found no differences between the phase. One apparent consideration for not doing screening seems to be primarily "economic":

> If scheduling surgery is dependent on the hormonal status of the patient then the available window for surgery becomes more limited, which will place increased logistical demands on the unit and surgeons performing breast cancer surgery, it is even possible that surgery may have to be delayed while waiting for the appropriate phase (Chaudhry et al., 2006).

The effects of progesterone on the vascular system are less well known and still a matter of debate. Natural progesterone did not show vascular toxicity in a study using video microscopic recording of blood flow, blood vessel morphology and activities of various blood cells in live animals (Thomas et al., 2003). In other studies, progesterone and selective 19-norprogesterone derivatives were found not to interfere with estrogen protection against vasoconstriction (Adams et al., 1990; Wagner et al., 1991; Williams et al., 1998; Koh & Sakuma, 2004). However, there has been some concern with high doses of progesterone (Hanke et al., 1996a, 1996b).

Again, as for the nervous system and the breast, serious concerns have been raised about the use of synthetic progestins, and in particular of MPA, for which vascular toxicity has been reported. In both peripheral and cerebral vasculature, synthetic progestins were shown to cause endothelial disruption, accumulation of monocytes in the vessel wall and platelet activation (Thomas et al., 2003). There are many other reports of negative effects of MPA on the vascular system (Williams et al., 1994; Adams et al., 1997; Miyagawa et al., 1997; Williams et al., 2002; Miller et al., 2003).

6. Progesterone signaling in the nervous system

The multiple mechanisms of action of progesterone and its metabolites comprise the regulation of gene transcription, the modulation of neurotransmitter receptors and the activation of signaling cascades via membrane receptors (Mani & O'Malley, 2002; Schumacher & Robert, 2002; Li & O'Malley, 2003; Lösel et al., 2003; Pettus et al., 2005; Mani, 2006). These different signaling mechanisms, in particular the recognition of the significance of nuclear coregulator proteins in regulating the transcriptional activity of steroid receptors, and the cloning of new membrane steroid receptors offer novel perspectives for the development of selective neuroprotective progestins.

6.1. Progesterone receptor isoforms and nuclear coactivators

The transcriptional effects of progesterone, also referred to as "genomic" or "classical" effects, are mediated by at least 2

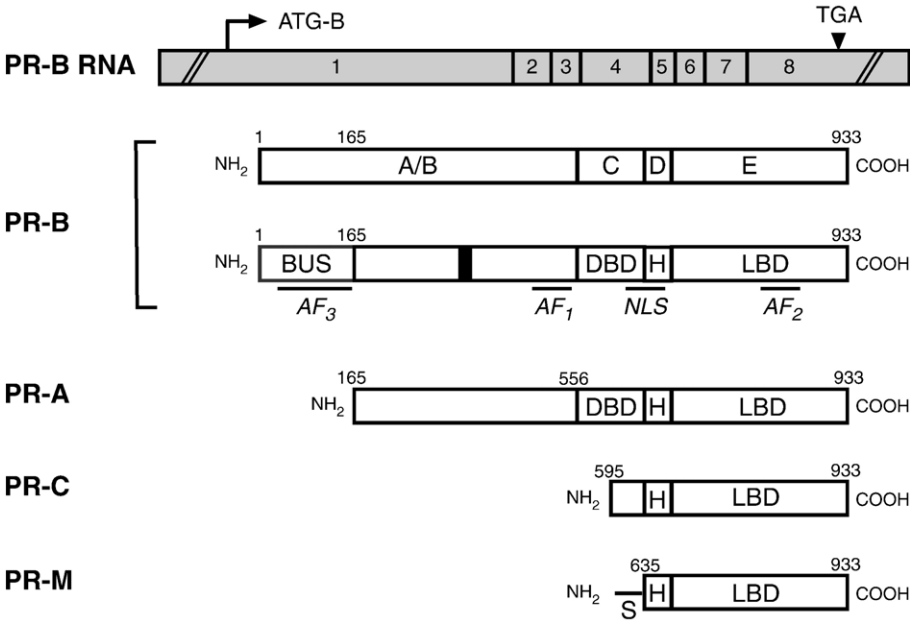

Fig. 2. Schematic presentation of 4 different PR isoforms. PR-A, PR-B, PR-C and PR-M are encoded by a single gene and result from the use of different transcription or translation start sites. The cDNA of PR-B is presented on top and shows the 8 exons which encode the different functional domains (**A**–**E**) of the PR-B protein presented just below. Exon 1 encodes the A/B domain (N-terminal domain), exons 2 and 3 the C domain (DNA binding-domain, LBD), exons 4–8 the D domain (hinge region, H) and the E domain (ligand binding-domain, LBD). AF1–3 correspond to distinct activation domains, to which coactivators bind. The nuclear localization signal (NLS) extends over the hinge region and the DBD. The PR-B and PR-A isoforms differ by an N-terminal 164-amino acid segment called BUS (B-receptor upstream segment). PR-C lacks 1 of the 2 zinc fingers and PR-M has no DBD. As a consequence, both PR-C and PR-M may only modulate transcription by direct interactions with other nuclear proteins (Misrahi et al., 1993; Wei et al., 1996; Saner et al., 2003; Takimoto et al., 2003).

intracellular receptor isoforms (PR-A and PR-B) but the existence of additional isoforms has been strongly suggested (Fig. 2). The PR-A and PR-B isoforms are generated from a single gene and differ only by an additional 164 amino acid segment in the N-terminal region of PR-B (Kastner et al., 1990; Conneely & Lydon, 2000; Takimoto et al., 2003). In vitro studies have provided evidence that PR-A and PR-B display distinct transactivational properties (Meyer et al., 1992; Vegeto et al., 1993; Horwitz et al., 1995; Dijkema et al., 1998; Hovland et al., 1998). Moreover, in a promoter- and cell-specific manner, PR-A has been shown to repress the transcriptional activity of PR-B and the other steroid receptors, an effect which has been qualified as "transrepression" (Vegeto et al., 1993; Wen et al., 1994; Kraus et al., 1995; Abdel-Hafiz et al., 2002).

The creation of mice selectively lacking either PR-A or PR-B has confirmed that the 2 PR isoforms function as distinct transcription factors and mediate different but partially overlapping reproductive responses to progesterone (Conneely et al., 2002). Female mice lacking PR-A have normal mammary glands but display severe ovarian abnormalities and uterine hyperplasia and are infertile. In contrast, the inactivation of PR-B resulted in reduced pregnancy-associated mammary ductal morphogenesis but did not affect ovarian and uterine development, consistent with the observation that PR-A is sufficient for the establishment and maintenance of pregnancy (Mulac-Jericevic et al., 2000; Mulac-Jericevic & Conneely, 2005).

However, the respective functions of PR-A and PR-B in the nervous system, and their roles in mediating the trophic and protective effects of progesterone, remain to be explored. It is known only that the regulation of PR-A and PR-B expression varies between different brain regions according to sex, hormonal status and age (Kato et al., 1993; Camacho-Arroyo et al., 1994; Szabo et al., 2000; Inoue et al., 2001; Guerra-Araiza et al., 2002; Beyer et al., 2002). In addition to PR-B and PR-A, other PR transcripts have been identified in malignant progesterone target tissues or cloned from cDNA libraries (Richer et al., 1998; Balleine et al., 1999; Misao et al., 2000; Hirata et al., 2003; Fig. 2). Their presence and biological significance in the nervous system have never been studied.

The discovery of nuclear steroid receptor coregulators, comprising coactivators, and corepressors has opened new avenues of research into the genomic effects of steroid hormones. The number of coregulators which can be recruited by steroid and other nuclear receptors is continuously increasing, and their cell-, promoter- and ligand-specific actions have been extensively reviewed (McKenna et al., 1999; McKenna & O'Malley, 2002; Kalkhoven, 2004; Pearce et al., 2004; Privalsky, 2004; Smith & O'Malley, 2004; Lonard & O'Malley, 2005; Mahajan & Samuels, 2005; Wu et al., 2005). Agonist binding is believed to increase the affinity of steroid receptors for coactivators, providing the conditions for efficacious transcriptional activation. Coactivators include molecules which facilitate the access of the basal transcriptional machinery to gene promoters, such as histone acetyltransferase (HAT) coactivators. The acetylation of histone lysines disrupts molecular interactions, which maintain gene promoters in a "closed" state. The best characterized groups are the p160 (the steroid receptor coactivators SRC-1a, SRC-1e, SRC-2 and SRC-3) and the CBP/p300 families, which act in concert with other factors and bring HAT activity to the vicinity of steroid receptor complexes (Fig. 3). Unfortunately, a heterogeneous nomenclature is in

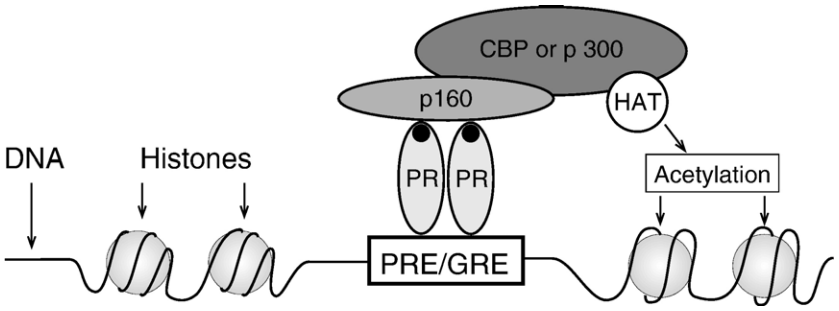

Fig. 3. The recruitment of coactivators by PR. The liganded PR bind as homodimers to progesterone/glucocorticoid response elements (PRE/GRE), generally located in the promoter regions of target genes, and recruit nuclear coactivator proteins. Coactivators include molecules that facilitate the access of the basal transcriptional machinery to gene promoters, such as HAT coactivators. The acetylation of histone lysines disrupts molecular interactions, which maintain gene promoters in a "closed" state. The best characterized groups of coactivators are the p160 (SRC) and the CBP/p300 families.

use for the p160 coactivators (SRC-1 = NCoA-1; SRC-2 = NCoA-2 or GRIP1 or TIF-2; SRC-3 = p/CIP, ACTR, TRAM-1 or RAC-3) (Onate et al., 1995; Hong et al., 1997; Gehin et al., 2002). For reasons of clarity, the SRC nomenclature is exclusively used here. It should also be emphasized that numerous other coactivator complexes are involved in bridging the RNA polymerase II complex with basal transcription factors (Nishihara et al., 2004; Lonard & O'Malley, 2005).

Important functions of the SRC in PR-mediated reproductive functions have been revealed by the study of SRC KO mice. Thus, SRC-2 and SRC-1 cooperate in the progesterone-dependent decidualization of the mouse uterus, whereas SRC-3 KO is involved in parity-associated development of the mammary gland (Xu et al., 1998a, 2000; Mukherjee et al., 2006). Again, as for the PR isoforms, only a few studies have examined the functional relationship between steroid receptors and their coregulators in the nervous system, in spite of the fact that steroid receptor coactivators are expressed throughout the nervous system. Knock-out mouse models for individual members of the p160 coactivators show only minor phenotypic defects, such as partial hormone resistance and a delay in the development of cerebellar Purkinje cells, suggesting functional redundancy between coactivators in nervous tissues (Xu et al., 1998b; Nishihara et al., 2003). However, in contrast to the KO models, the stereotaxic injection of antisense oligodeoxynucleotides into the brain, allowing the expression of specific coactivators to be decreased in a time- and region-specific manner has demonstrated the critical role of nuclear coactivators in steroid receptor signaling. Thus, infusion of SRC-1 or CBP antisense oligodeoxynucleotides into the rat brain impaired the process of steroid-dependent sexual differentiation of brain structures and inhibited progesterone-facilitated sexual receptivity in females (Auger et al., 2000, 2002; Molenda et al., 2002). Antisense oligodeoxynucleotides to SRC-1 and SRC-2 but not to SRC-3, inhibited lordosis behavior and the induction of the PR by estrogen within the ventromedial hypothalamus in rats and mice, consistent with the presence of SRC-1 and SRC-2 and the absence of SRC-3 within this brain region (Apostolakis et al., 2002). That coactivators are limiting factors in steroid responses in the brain has been clearly demonstrated in a recent study showing a critical role for SRC-1 in mediating reproductive function of testosterone within the preoptic area (Charlier et al., 2005).

The actions of the classical PR have been shown to be even more complex with the discovery that the receptors are not only targeted to the nucleus but also to the cell membrane, where they interact with other proteins belonging to intracellular signaling pathways (Edwards, 2005). Thus, the N-terminal domain common to PR-A and PR-B selectively interacts with Src tyrosine kinase family members. Interactions of the PR with the SH3 domain of these signaling molecules was found to be transient and ligand-dependent, and is a unique feature of the PR (Boonyaratanakornkit et al., 2001; Edwards et al., 2003). A functional consequence of PR interaction with the SH3 domain of Src kinase is the activation of the Src/Ras/MAPK (mitogen-activated protein kinase) signaling pathway, as has been demonstrated in MCF-7 breast cancer cells (Migliaccio et al., 1998; Leonhardt et al., 2003).

6.2. The modulation of neurotransmitter receptors

The inhibition of neuronal excitability is an important component of the neuroprotective effects of progesterone and its metabolites. In this regard, they differ from the estrogens, which in general exert excitatory effects by potentiating the actions of excitatory neurotransmitters (Smith & Woolley, 2004). As already mentioned, progesterone inhibits the activity of neuronal nAChR but only at high micromolar concentrations (Valera et al., 1992; Léna & Changeux, 1993). The other target for progesterone, the σ1 receptor, was first defined by its ability to bind with high affinity a variety of pharmacologically active drugs, termed "sigma ligands" (Quirion et al., 1992; Bastianetto et al., 1999). It has since been cloned from guinea pig liver microsomes, a human placental cell line, mouse kidney, and a rat brain cDNA library (Hanner et al., 1996; Kekuda et al., 1996; Prasad et al., 1998; Seth et al., 1998). It has been proposed that this endoplasmic reticulum-anchored protein may, upon activation, translocate to the vicinity of the cell membrane, where it may regulate signal transduction (Morin-Surun et al., 1999). Progesterone acts as a competitive inhibitor of σ1 receptor agonist binding (Su et al., 1988; McCann et al., 1994; Hanner et al., 1996). A role for the inhibition of σ1 receptor functions by progesterone has been documented in the dorsal hippocampus. Thus, the potentiation of the *N*-methyl-D-aspartate (NMDA) response of hippocampal neurons and the

NMDA-evoked norepinephrine release from preloaded hippocampal slices by σ1 ligands, were both strongly reduced in the presence of progesterone (Monnet et al., 1995; Debonnel et al., 1996; Bergeron et al., 1999). Furthermore, progesterone has been shown to influence the behavioral efficacy of σ1 receptor ligands in mice (Phan et al., 2002; Maurice, 2004).

The most studied membrane effect of a progestagen is the positive modulation of $GABA_A$ receptor activity by allopregnanolone, which explains some of the psychopharmacological effects of the steroid (Majewska et al., 1986; Belelli et al., 2002). The enantioselectivity of the effects of allopregnanolone on $GABA_A$ receptors and the recent development of a selective inhibitor of the GABA modulatory effects of 5α-pregnane steroids are in favor of the existence of specific steroid binding sites (Covey et al., 2001; Mennerick et al., 2004). In fact, a recent study has demonstrated the presence of 2 discrete steroid binding sites on $GABA_A$ receptors. Allopregnanolone potentiates GABA responses by binding to a cavity located between the transmembrane domains M1 and M4 of α subunits, whereas it directly activates $GABA_A$ receptors by binding to interfacial residues between α and β subunits (Hosie et al., 2006).

The formation of allopregnanolone also plays an important role in the neuroprotective and promyelinating actions of progesterone. Thus, after TBI, the administration of allopregnanolone has antiapoptotic and antiastrogliotic effects and improves cognitive recovery (He et al., 2004; Djebaili et al., 2005). This is consistent with the GABAergic innervation of the 2 brain nuclei, namely the MDN and NBM, where secondary neuron loss takes place after TBI. Potentiation of inhibitory GABAergic transmission by allopregnanolone may preserve neurons from the effects of excessive excitatory neurotransmitter release in response to injury. Most importantly, the 3β,5α-reduced isomer epiallopregnanolone, which is inactive at $GABA_A$ receptors, neither reduced secondary neuronal loss nor improved behavioral recovery in this model. Allopregnanolone also attenuated neuronal death in the cerebral cortex after experimental cerebral infarction and in the hippocampus after excitotoxic injury (Ciriza et al., 2004a, 2004b; He et al., 2004; Sayeed et al., 2006). In culture, mouse P19 neurons were protected by allopregnanolone against NMDA-induced apoptosis (Xilouri & Papazafiri, 2006). Allopregnanolone has also recently been shown to stimulate the proliferation of cerebral and hippocampal neuroprogenitor cells via $GABA_A$ receptor-activated voltage-gated L-type calcium channels and to promote neurogenesis (Wang et al., 2005; Brinton & Wang, 2006).

The modulatory effect of allopregnanolone on $GABA_A$ receptors also plays a role in myelin formation. Thus, in organotypic cultures of cerebellar slices taken from postnatal rats or mice, progesterone accelerated myelination via 2 signaling systems: the intracellular PR and membrane $GABA_A$ receptors (Ghoumari et al., 2003). That is, as already mentioned, progesterone had no effect on myelination in slices prepared from PR KO mice, thus demonstrating a key role for the intracellular receptors. However, progesterone was also metabolized in the cerebellar slices to allopregnanolone, and inhibition of this metabolic pathway by the 5α-reductase inhibitor L685-273 significantly reduced the promyelinating effect of progesterone. Moreover, myelination could also be stimulated by adding allopregnanolone to the culture medium, and this effect could be blocked by the selective $GABA_A$ receptor antagonist bicuculline (Ghoumari et al., 2003).

An advantage of these organotypic cultures is that they represent an integrated system which closely reproduces developmental events, thus providing a unique model for examining neuronal maturation and the myelination of axons (Dusart et al., 1997; Ghoumari et al., 2002). However, they do not allow a determination as to whether progesterone and allopregnanolone promote myelination by acting on oligodendrocytes or neurons. Nevertheless, a direct effect of allopregnanolone on the proliferation of oligodendrocyte preprogenitor cells has been demonstrated, involving 2 autocrine regulatory loops. PSA-$NCAM^+$ neural progenitors isolated from neonatal rat brain, which are still multipotent but spontaneously differentiate into oligodendrocytes when grown in culture, were shown to synthesize both allopregnanolone and GABA. The latter stimulated progenitor proliferation through a $GABA_A$ receptor-mediated mechanism, and its mitogenic effect was potentiated by allopregnanolone (Gago et al., 2001, 2003, 2004). A direct effect of allopregnanolone on myelinating glial cells has been demonstrated in the PNS. Cultured Schwann cells express $GABA_A$ receptor subunits, which may form functional receptor complexes involved in the upregulation of specific peripheral myelin proteins by allopregnanolone (Magnaghi et al., 2001).

However, not all of allopregnanolone's effects are necessarily mediated by $GABA_A$ receptors as has been shown for its neuroprotective actions in the NP-C mouse, a murine model of Niemann-Pick type C disease, characterized by neurological deficits and Purkinje cell loss. In these mice, levels of allopregnanolone are decreased, as is the expression of the enzymes involved in its synthesis, especially in the cerebellum. Most importantly, the systemic administration of allopregnanolone significantly delayed the onset of neurological symptoms and prolonged Purkinje cell survival (Griffin et al., 2004). These neuroprotective effects of allopregnanolone may have been blocked by bicuculline, an antagonist specific to $GABA_A$ receptors. Thus, they seemed to be mediated, at least in part, by $GABA_A$ receptors. However, it was recently shown that the beneficial effects of allopregnanonolone could be mimicked by its enantiomer (*ent*-allopregnanolone), which is inactive at $GABA_A$ receptors. Moreover, the efficacy of allopregnanolone and *ent*-allopregnanolone correlated with their ability to activate pregnane X receptor (PXR)-dependent gene expression (Langmade et al., 2006). These findings point to a role for PXR in mediating part of the neuroprotective effects of allopregnanolone.

It is interesting to note that most studies which have examined the role of the 5α-reduced metabolites of progesterone have focused on allopregnanolone. Moreover, inhibition by pharmacological or transgenic means of the 5α-reductases, enzymes which convert progesterone to 5α-dihydroprogesterone (5α-DHP), is generally accepted as a proof for the importance of allopregnanolone formation. This is not taking into account that 5α-DHP, whose formation is also blocked by the inhibitors, may exert important specific actions on its own,

as it can also activate gene transcription by binding to the PR (Rupprecht et al., 1993; Finn et al., 2006; Fig. 1).

This situation contrasts with studies performed on the 5α-reduction of testosterone, which is catalyzed by the same enzymes. Indeed, inhibition of the 5α-reductases is commonly used to prevent the actions of 5α-dihydrotestosterone (5α-DHT), which has up to 10 times greater affinity for the AR than testosterone, and thus serves as a signal amplification (Mahendroo et al., 2001). In addition, it cannot be excluded that T and 5α-DHT may exert distinct transcriptional effects, although this concept awaits further experimental evidence (Hsiao et al., 2000; McPhaul, 2003).

Whereas 5α-DHT has much higher affinity for the AR than testosterone, 5α-DHP has in general less affinity than progesterone for the PR, as shown for different species including rat, mouse, rabbit, sheep, dog, monkey and humans; the only known exception being the chicken receptor (Kontula et al., 1975; Illingworth et al., 1977; Roselli & Snipes, 1983; Rupprecht et al., 1996; Marinelli et al., 2004). Consistently, 5α-DHP has been shown to be much less efficient than progesterone in transactivating a typical progesterone-sensitive promoter; the mouse mammary tumor virus (MMTV) promoter, via the human PR-B transfected into neuroblastoma cells (Rupprecht et al., 1993).

However, a few reports suggest specific biological effects of 5α-DHP (Karavolas et al., 1984). Thus, in the nervous system, 5α-DHP regulates expression of the peripheral myelin protein P0 in Schwann cells and of the intermediary filament GFAP in astrocytes (Melcangi et al., 1996; Martini et al., 2003; Morita et al., 2006). The control of P0 expression by 5α-DHP has been shown to require recruitment of SRC-1 (Cavarretta et al., 2004). That 5α-DHP may have different biological effects than progesterone has also more recently been demonstrated for breast cancer cells; the metabolite was shown to stimulate the proliferation and detachment of cells by acting via membrane sites linked to the MAPK pathway (Wiebe, 2006; Wiebe et al., 2006).

6.3. Membrane receptors of progesterone

The characterization of membrane binding sites for progesterone has always been tentative (Tischkau & Ramirez, 1993). It was only 10 years ago that a first putative membrane receptor of progesterone, distinct from the classical PR isoforms and comprising 194 amino acids with a single membrane-spanning domain, was isolated and cloned from porcine liver (Falkenstein et al., 1996; Meyer et al., 1998). Subsequently, homologous proteins were cloned in rat (named 25-Dx), cattle and humans (Lösel & Wehling, 2003). The term 25-Dx has been used in recent studies describing the expression and regulation of this membrane receptor in the brain and spinal cord (Krebs et al., 2000; Labombarda et al., 2003; Sakamoto et al., 2004; Meffre et al., 2005). However, the protein is now referred to by some as "progesterone membrane receptor component 1" (PGRMC1) (Lösel et al., 2004), and this nomenclature will be adopted here.

Earlier studies suggested that PGRMC1 may be associated with endomembranes rather than plasma membranes (Falkenstein et al., 1999). However, recent studies in the rat ovary have cast new light on the subcellular localization and the significance of PGRMC1. There, PGRMC1 mediates the anti-apoptotic actions of progesterone in both granulosa and luteal cells. In the granulosa cells, PGRMC1 localizes to the nuclei but after treatment of the cells with human chorionic gonadotropin (hCG), it is almost exclusively present at the plasma membrane (Peluso, 2006). At the level of the plasma membrane, PGRMC1 interacts with another membrane protein, the plasminogen activator inhibitor RNA binding protein-1 (PAIRBP1, also known as RDA288 or SERBP1), and forms a complex required for transducing the antiapoptotic actions of progesterone in the ovary (Peluso et al., 2006). The elucidation of the signal transduction pathway of the PGRMC1–PAIRBP1 progesterone membrane receptor complex in the ovary has just begun and may involve increased cGMP and activation of protein kinase G (PKG) (Engmann et al., 2006). The cytoplasmic domain of PGRMC1 also has several potential Src homology 2 and Src homology 3 domains, through which progesterone activation could transduce an intracellular signal (Peluso, 2006).

The presence of PGRMC1 has also been described on the cell surface of hypothalamic and spinal neurons (Krebs et al., 2000; Labombarda et al., 2003). However, its signaling mechanisms have still not been studied in the nervous system. The distribution and regulation of PGRMC1 within different compartments of the nervous system may provide some clues to its functions. In the ventromedial hypothalamus of female rats, expression of PGRMC1 was shown to be increased by estrogen treatment, and the protein may thus play a role in the activation of female sexual behavior (Krebs et al., 2000). A detailed immunohistochemical study of the distribution of PGRMC1 in the rat brain has confirmed the presence of the protein in the hypothalamus and has demonstrated its expression in circumventricular organs and ependymal cells of the ventricular walls as well as in vasopressin neurons of the paraventricular, supraoptic and retrochiasmatic nuclei. Together with the observations that PGRMC1 was up-regulated in neurons and induced in astrocytes after TBI, these findings strongly suggest that the progesterone-binding protein has a role in the maintenance of the water balance after injury (Meffre et al., 2005). A role of PGRMC1 in mediating protective effects of progesterone in the nervous system is also supported by the observation that its mRNA and protein were up-regulated by progesterone treatment in dorsal horn neurons of spinal cord-injured male rats (Labombarda et al., 2003). In the cerebellum, PGRMC1 is present in Purkinje cells and in the external granule cell layer. The protein is particularly abundant during early postnatal life, suggesting a role in developmental processes (Sakamoto et al., 2004).

In 2003, an entire group of progesterone membrane receptors (mPR) was cloned from fish oocytes (Zhu et al., 2003; Zhu & Thomas, 2003). Unrelated to known nuclear steroid receptors, the mPRs meet all the criteria of true membrane receptors, including the structure of a membrane-spanning protein, plasma membrane localization, expression in steroid target tissues, selective steroid binding, regulation of intracellular signaling pathways, and regulation by hormones and biological functions.

In the spotted sea trout, the first mPR gene cloned was found to be selectively expressed in reproductive endocrine tissues and in brain. Computer modeling predicted a protein with 7 transmembrane domains, characteristic of G protein-coupled receptors. In fact, the fish mPR was shown to activate a pertussis toxin-sensitive inhibitory G protein, to inhibit adenylate cyclase activity, and to activate the MAPK pathway, thus resembling membrane actions of progesterone described 25 years ago in Xenopus oocytes (Finidori-Lepicard et al., 1981).

Subsequently, 13 new genes closely related to the fish mPR have been cloned from several vertebrate species including human, mouse and pig (Zhu & Thomas, 2003; Thomas et al., 2004). They all encode proteins with 7 transmembrane domains, with the characteristics of G protein-coupled receptors, and belong to a large and ubiquitous family of proteins found in both prokaryotes and eukaryotes, termed progestin and adiponectin receptors (PAQR; Lyons et al., 2004; Fernandes et al., 2005). The expression and regulation of these new membrane receptors has begun to be explored in the mammalian reproductive tract but still not in the nervous system. A recent study has provided evidence for the expression and regulation of mPR in the rat corpus luteum, a tissue that interestingly does not contain detectable levels of intracellular PR but where actions of progesterone may be mediated by membrane receptors (Cai & Stocco, 2005). Very recently, the presence of both mPRα and mPRβ has been demonstrated in human myometrium, where the activation of the mPR leads to transactivation of PR-B and to a decrease in SRC-2 expression, pointing to a possible cross-talk between membrane and nuclear receptors of progesterone (Karteris et al., 2006). As the study of membrane receptors of progesterone, including PGRMC1 and the mPR, is a very recent field, and it is thus not surprising that some controversies are being raised (Krietsch et al., 2006).

Whatever, the novel membrane receptors are likely to provide new opportunities for the development of receptor ligands specifically targeting the cell plasma membrane. A very recent study has indeed shown that the binding characteristics of the human mPRα are very distinct from those of the classical PR. In stably transfected human MDA-MB-231 cells, human mPRα localized to the plasma membrane and bound with high affinity and selectivity progesterone (Kd ≈ 7 nM). However, in contrast to the classical PR, the recombinant hu-mPRα did not bind progestins commonly used as contraceptives or in HRT, and it had no affinity for the PR antagonist mifepristone (RU486) and for the very selective PR agonist Organon-2058. Thus, the human mPRα shows a specific pharmacological profile, distinct from that of the classical PR (Thomas et al., 2007).

6.4. The influence of the pathophysiological state

There is evidence that steroid actions in the nervous system may involve different signaling mechanisms depending on the pathophysiological context. Steroids may exert different actions and use different signaling mechanisms in the normal, injured, and perhaps in aged nervous tissues.

It has already been mentioned that $GABA_A$ receptors may become excitatory in response to seizures or injury, and as a consequence that the actions of the GABA-active steroid allopregnanolone on neuronal activity may shift from inhibitory to excitatory. In progesterone-treated male rats, expression of PGRMC1 is increased in the dorsal horns of the transected spinal cord. In contrast, the classical PR was down-regulated under these conditions (Labombarda et al., 2003). Also, in response to TBI, expression of PGRMC1 was upregulated in neurons and induced in astrocytes (Meffre et al., 2005), suggesting that this putative membrane receptor of progesterone may play an important role in the hormone's neuroprotective effects. Significantly, some genes of the CNS involved in neuronal functions become sensitive to progesterone only after injury (De Nicola et al., 2003; Schumacher et al., 2004).

Another example of alternative receptor signaling pathways in the injured nervous system concerns the putative estrogen membrane receptor ER-X, which is present in cortical and uterine plasma membranes of postnatal but not of adult animals, suggesting important functions in developmental processes. However, ER-X is again expressed following ischemic brain injury, and may thus play a role in mediating the neuroprotective and neurotrophic effects of estrogen in the adult nervous system (Toran-Allerand et al., 2002).

7. Progesterone present in the nervous system: different sources

7.1. Peripheral sources

The endogenous progesterone which confers protection to cycling and pseudopregnant female rats against edema and neurodegeneration after TBI is mainly derived from the corpus luteum (in contrast to humans, in rodents the ovary is the main source of progesterone during pregnancy and the placenta synthesizes only small amounts; Sanyal, 1978; Arensburg et al., 1999). Progesterone easily crosses the blood–brain barrier and diffuses throughout nervous tissues. The very strong protection provided by high levels of ovarian progesterone in females does not preclude the possibility that progesterone originating from other sources also contributes to neuroprotection. Even in males, which are much more vulnerable to brain injury compared with females, low levels of endogenous progesterone, either secreted by the adrenal glands or synthesized within the nervous system, may have beneficial effects and improve the outcome of injury to some extent. But endogenous progesterone in males is clearly not sufficient to reach the degree of neuroprotection observed in females, and hormone supplementation is beneficial. As discussed below, an alternative strategy would be to increase the low endogenous production of progesterone.

Secretion of progesterone by the adrenal glands is under the control of adrenocorticotropic hormone (ACTH; Resko, 1969; Feder & Ruf, 1969). As a consequence, the production of progesterone by the adrenal glands is increased in response to stress and can reach noticeable levels (Fajer et al., 1971; Huang et al., 1976). In women, some serum progesterone is derived from the adrenal glands, whereas in men, plasma progesterone is exclusively of adrenal origin (Gutai et al., 1977; Eldar-Geva et al., 1998; Puder et al., 2000).

7.2. Nervous system-derived progesterone

Progesterone is also synthesized by neurons and glial cells within the CNS and PNS. Steroids which are synthesized within the nervous system de novo from cholesterol have been named "neurosteroids" (Baulieu, 1981; Baulieu et al., 2001). From an evolutionary point of view, progesterone is synthesized within the nervous system of all species studied so far, and the 3β-HSD enzymes, necessary for the conversion of pregnenolone to progesterone, are widely distributed throughout the brains of fishes, amphibians, birds and mammals (Mensah-Nyagan et al., 1994; Guennoun et al., 1995; Usui et al., 1995; Robel et al., 1999; Ukena et al., 1999; Tsutsui et al., 2000; Hu et al., 2001; Sakamoto et al., 2001; Mellon & Vaudry, 2001; Mensah-Nyagan et al., 2001). There are multiple isoforms of the 3β-HSD encoded by different genes (Simard et al., 2005). The genes of 2 3β-HSD isoenzymes have been cloned in humans: the type I 3β-HSD gene (*HSD3B1*), predominantly expressed in placenta and peripheral tissues including the mammary gland and skin, and the type II 3β-HSD gene (*HSD3B2*), expressed in the gonads, adrenal glands and brain (Simard et al., 1996; Inoue et al., 2002; Simard et al., 2005). Multiple 3β-HSD isoenzymes have been cloned from several other species: 4 members of the rat and 6 members of the mouse 3β-HSD family (Payne et al., 1997; Peng et al., 2002). Unfortunately, for each of these species, 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.

The synthesis of neurosteroids in the rodent nervous system has been extensively reviewed (Robel et al., 1999; Baulieu et al., 2001; Mellon & Vaudry, 2001; Tsutsui, 2006). The mitochondrial cytochrome P450scc, the cholesterol side chain cleavage enzyme which catalyzes the de novo synthesis of pregnenolone, is expressed at low levels throughout the rodent brain and has been detected in most cell types (Mellon & Deschepper, 1993; Sanne & Krueger, 1995; Strömstedt & Waterman, 1995; Kohchi et al., 1998; Robel et al., 1999; Mellon et al., 2001). Its presence and activity have recently been studied within pain pathways, and results suggest an important role of locally synthesized progesterone and allopregnanolone in the control of pain mechanisms (Patte-Mensah et al., 2003; Patte-Mensah et al., 2005; Poisbeau et al., 2005). The second enzyme necessary for the synthesis of progesterone, the 3β-HSD, is also present in neurons and glial cells. The enzyme is present in the cytoplasm but also forms a catalytically active molecular complex with the cytochrome P450scc at the inner mitochondrial membrane (Cherradi et al., 1995). Detailed in situ hybridization studies have shown its widespread expression in the rat CNS during development and adulthood (Guennoun et al., 1995; Coirini et al., 2002; Ibanez et al., 2003a). The synthesis and functions of progesterone have been extensively studied in Purkinje cells (Tsutsui et al., 2003).

Evidence has accumulated over the past few years that progesterone and its metabolites are also synthesized in the human nervous system (Beyenburg et al., 2001; Stoffel-Wagner, 2001; Schumacher et al., 2003; Weill-Engerer et al., 2003). The presence of cytochrome P450scc was first detected in the human brain by immunocytochemistry (Le Goascogne et al., 1989) and subsequently several studies have described the presence of P450scc mRNA in different brain regions (Beyenburg et al., 1999; Watzka et al., 1999; Inoue et al., 2002; Yu et al., 2002). The type II isoform of the human 3β-HSD is largely expressed in different parts of the brain and spinal cord (Inoue et al., 2002; Yu et al., 2002), and the enzymes necessary for the metabolism of progesterone are also present in the human brain (Steckelbroeck et al., 2001; Stoffel-Wagner et al., 2003).

A recent study has shown that an increase in pregnenolone and progesterone synthesis within the spinal cord is part of the response to injury, consistent with an important role of these neurosteroids in the protection and regeneration of nerve cells (Labombarda et al., 2006b). In this study, the effects of spinal cord transection on neurosteroid levels and on the expression of steroidogenic enzymes were analyzed in male rats deprived of their steroidogenic endocrine glands by castration and adrenalectomy. Steroid levels were quantified by gas chromatography/mass spectrometry (Liere et al., 2000, 2004). In the absence of circulating steroids, significant levels of pregnenolone, progesterone and allopregnanolone persisted in the spinal cord, and were significantly increased in response to injury. Interestingly, there was an increase in pregnenolone as early as 24 hr after injury, followed at 75 hr by an increase in progesterone. These observations are consistent with a sequential increase in pregnenolone and progesterone biosynthesis in response to injury. Moreover, high levels of allopregnanolone were detected in the spinal cord, whereas its plasma levels remained barely detectable, suggesting a local synthesis of this metabolite (Labombarda et al., 2006b).

Expression of 3β-HSD and levels of progesterone were also strongly upregulated in the brains of dysmyelinating jimpy and shiverer mouse mutants (Le Goascogne et al., 2000) and in the spinal cord of streptozotocin treated diabetic rats (Saredi et al., 2005). Neuropathic pain has also been shown to increase the neosynthesis of pregnenolone and allopregnanolone in the rat spinal cord, consistent with a role for these neurosteroids in nociception and neuroprotection (Patte-Mensah et al., 2006; Schlichter et al., 2006). All these observations provide strong evidence that an increase in the synthesis of progesterone and its metabolites may be part of the mechanisms by which nerve cells cope with neurodegeneration.

8. Therapeutic perspectives for progestagens

Two therapeutic approaches derive from the multiple effects and actions of progesterone in the nervous system: (1) the administration of progestins which have a selective activity on specific nervous functions; (2) stimulation of the local synthesis of progesterone and its metabolites in the nervous system, preferably at lesion sites.

8.1. Selective progestins

The variety of mechanisms by which progestagens exert their effects in the nervous system, including genomic and rapid membrane actions, offer enormous possibilities for the development of more efficient and safe treatments. Laboratories

are searching for chemical modifications of progestagens and estrogens to eliminate the side effects associated with chronic hormone use, in particular endocrine disturbances, while enhancing their beneficial effects on the nervous system. Novel steroid compounds with potential interest for neuroprotection and neuroregeneration are the selective progesterone receptor modulators (SPRM), which, like the selective estrogen receptor modulator (SERM), show tissue-specific mixed agonist-antagonist properties (Brinton, 2004; Vogelvang et al., 2004; Chabbert-Buffet et al., 2005).

Mifepristone, which like other SPRM behaves as either a PR agonist or antagonist under different conditions (Beck et al., 1993; Nordeen et al., 1993; Sartorius et al., 1993), has been shown to protect Purkinje cells from postnatal or pathological apoptotic death (Ghoumari et al., 2003). Interestingly, the neuroprotective effect involved neither PR nor GR, because it could not be mimicked or inhibited by other ligands of these receptors, and because it still took place in PR KO mice and in brain-specific GR mutant mice ($GR^{Nes/Cre}$). Mifepristone was then shown to down-regulate expression of the Na^+, K^+ -ATPase and to cause depolarization of the Purkinje cell membrane, suggesting a critical role for excitatory inputs in Purkinje cell survival during early postnatal development (Ghoumari et al., 2006). These findings reveal a new neuroprotective mechanism of a steroid compound, which may guide the development of new therapeutic approaches for maintaining the resting potential of neurons at values favorable for their survival.

Enantiomers of steroids have also aroused much interest for neuroprotection and for treating neurodegenerative diseases (Akwa et al., 2001; Simpkins et al., 2004). Enantiomers are mirror-symmetric, non-superimposable images of a molecule, with identical physical properties except for the different rotation of polarized light. For example, the synthetic (−) enantiomer of pregnenolone sulfate was found to be 10 times more potent in activating memory functions than the natural (+) enantiomer. Interestingly, the promnesic effects of the (−) and (+) enantiomers of pregnenolone sulfate involved different mechanisms: in contrast to (+) pregnenolone sulfate, the promnesic effects of (−) enantiomer could not be blocked by a selective NMDA receptor antagonist (Akwa et al., 2001). Enantiomers of estradiol have also been produced, which have reduced binding to the classical intracellular ER but show increased neuroprotective activity, either in vitro models or after cerebral ischemia (Green et al., 2001; Yang et al., 2003; Simpkins et al., 2004).

It was thus a significant finding that administration of the enantiomer of progesterone (*ent*-progesterone) was efficient in decreasing cerebral edema, neuron death, inflammatory cytokines and reactive gliosis after TBI (Vanlandingham et al., 2006). Interestingly, the protective effects of *ent*-progesterone were not mediated by the intracellular PR, as the compound did not activate PR-mediated gene transcription, and its mechanisms of action, which may involve membrane receptors, need to be clarified. A previous study showed that *ent*-progesterone is a potent competitive inhibitor of the cytochromes P450c17 and P450c21, human enzymes involved in steroid metabolism (Auchus et al., 2003).

The development of selective and efficient PR antagonists is also needed for the treatment of some neurodegenerative conditions on which progesterone may have a negative influence. Thus, in a transgenic rat model of Charcot-Marie-Tooth disease (CMT-1A), an inherited peripheral neuropathy caused by enhanced expression of the peripheral myelin protein PMP-22, progesterone treatment caused a further increase in PMP-22, thus aggravating the clinical symptoms. Conversely, treatment with an antiprogestin had a beneficial influence on the evolution of the disease (Sereda et al., 2003). These findings are consistent with an earlier observation that progesterone increases the promoter activity of the *PMP-22* gene (Désarnaud et al., 1998).

An important emerging concept is that progestagens, and steroids in general, may use different signaling mechanisms in normal and injured nervous tissues. Thus, the transcriptional effects of steroids mediated by classical intracellular receptors may differ between normal and lesioned nervous tissues, either because of changes in receptor expression, their interaction with other co-operative signaling pathways or with nuclear coregulators. The observation of gene- and cell-specific recruitment of nuclear coregulators by steroid receptors has opened new opportunities for the selective regulation of steroid actions within the nervous system (Nishihara et al., 2004; Fonte et al., 2005; Grenier et al., 2006).

Membrane receptors of progesterone, whose expression is increased in response to lesion, are likely to mediate some of the hormone's protective and trophic effects. These novel membrane receptors need to be further characterized for the development of selective ligands. $GABA_A$ receptors are particularly interesting targets for progestins with neuroprotective membrane actions. Thus, selective agonists and antagonists for these receptors are developed (Reddy, 2003; Mennerick et al., 2004).

8.2. Stimulation of neurosteroid synthesis

Stimulating the local synthesis of progesterone may offer novel approaches to the treatment of lesions of the nervous system. This line of thinking receives support from observations that the formation of progesterone and its reduced metabolites is upregulated in the injured nervous system (Labombarda et al., 2006b). However, there are still serious gaps in our understanding of the regulatory mechanisms involved in the biosynthetic pathways of neurosteroids, some of which may be distinct from those described for the steroidogenic endocrine glands.

An intramitochondrial cholesterol transporter, the peripheral benzodiazepine receptor (PBR), offers promising possibilities for stimulating the synthesis of neurosteroids and promoting neuroprotection and neuroregeneration. Recently, the PBR has been renamed "translocator protein (18 kDa)" (TSPO) (Papadopoulos et al., 2006a), and this nomenclature will be adopted here. The TSPO is necessary for the transport of cholesterol from the outer to the inner mitochondrial membrane, where the cytochrome P450scc is located (Fig. 4). This represents a rate-limiting step in the biosynthesis of steroids (Papadopoulos, 1993; Papadopoulos et al., 2006b).

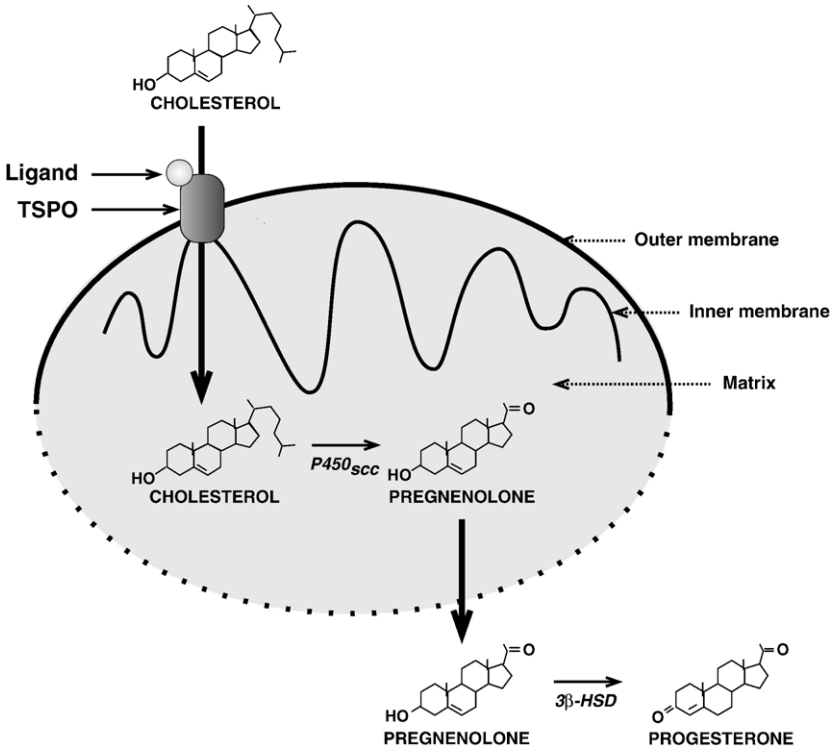

Fig. 4. Stimulation of progesterone synthesis by TSPO ligands. The TSPO (the former peripheral benzodiazepine receptor or PBR) is necessary for the transport of cholesterol from the outer to the inner mitochondrial membrane, where the cytochrome P450scc is located. This enzyme catalyzes the conversion of cholesterol to pregnenolone. Agonsits of the TSPO increase the intramitochondrial transport of cholesterol, which is a rate-limiting step in the biosynthesis of steroids. Pregnenolone is then metabolized to progesterone by the 3β-HSD.

Agonist ligands of TSPO make it possible to increase the synthesis of pregnenolone and progesterone in cultured glial cells and in the brain of castrated and adrenalectomized rats (Papadopoulos et al., 1992; Korneyev et al., 1993; Romeo et al., 1993; Bitran et al., 2000; Verleye et al., 2005). Interestingly, in response to injury, TSPO expression is increased in nervous tissues (Lacor et al., 1999; Garcia-Ovejero et al., 2005; Kassiou et al., 2005). A strong upregulation of TSPO expression has also been observed in degenerative diseases, such as Alzheimer's disease and multiple sclerosis (Vowinckel et al., 1997; Papadopoulos et al., 2006b). These observations suggest an increased sensitivity of lesioned or diseased nervous tissues to the effects of TSPO ligands, thus offering novel means for selective neuroprotection. TSPO ligands have been shown to protect neurons from excitotoxic injury, promote their regeneration, reduce inflammatory responses, decrease reactive gliosis and reduce aging-associated myelin degeneration (Ferzaz et al., 2002; Leonelli et al., 2005; Mills et al., 2005; Ryu et al., 2005; Veiga et al., 2005). However, a role for neurosteroids in mediating these beneficial effects of TSPO ligands still awaits demonstration. That is, TSPO ligands can influence many aspects of mitochondrial activity, not only steroidogenesis, as TSPO is physically associated with the voltage-dependent anion channel (VDAC) and the adenosine nucleotide translocase (ANT), which form the backbone of the mitochondrial permeability pore (Galiegue et al., 2003; Azarashvili et al., 2005).

Drugs other than those interfering with the intramitochondrial cholesterol transport have been shown to directly affect the biosynthesis or metabolism of progesterone. For example, antidepressants of the family of the "selective serotonin reuptake inhibitors" (SSRI), including fluoxetine (Prozac), sertraline (Zoloft) and paroxetine (Paxil), stimulated the formation of allopregnanolone by increasing the affinity of the human 3α-HSD type III for 5α-dihydroprogesterone. Sertraline also blocked the reverse oxidative reaction, the conversion of allopregnanolone to 5α-dihydroprogesterone (Griffin & Mellon, 1999).

9. Conclusions

The use of progestagens offers interesting therapeutic opportunities for treating the damaged nervous system: (1) they exert beneficial effects on 2 key processes involved in the maintenance and regeneration of nervous structures, namely, neuron viability and myelination; (2) their window for therapeutic intervention appears to be sufficiently large; (3) the blood–brain barrier is permeable to them; and (4) they are well tolerated.

The administration of natural progesterone, either orally in a micronized form or intravenously, may be recommended because it appears safe. Moreover, natural progesterone can be converted to neuroprotective metabolites, such as allopregnanolone. The 19-norprogesterone derivatives, which are very selective for the PR, also offer interesting possibilities, although they may not mimic all the effects of progesterone. Indeed, they are not metabolized to the same steroids as progesterone, and they may not activate the multiple receptor systems, in particular the membrane receptors, in the same manner as the natural

hormone. We still know very little about the pharmacological characteristics and signaling mechanisms of these novel receptors. Even the classical PR may acquire distinctive properties when it interacts with other proteins of cytoplasmic signaling cascades, or when it inserts into the plasma membrane. In contrast to progesterone and 19-norprogesterone derivatives, there are major concerns with the use of synthetic progestins cross-reacting with other steroid receptors and interfering with other beneficial steroid signaling pathways.

Although the use of natural progesterone is for the moment an interesting therapeutic option, the search for more selective, efficient and safe synthetic progestins remains an important objective. Indeed, both progesterone's pleiotropic effects and its multiple mechanisms of action offer interesting possibilities for the development of compounds which would ideally act on a subset of neural functions, for example myelination, axonal growth, neuronal excitability, anxiety or addiction, and produce unique physiological effects without undesired side effect activities, such as disturbing the classical endocrine functions of progesterone. Thus, there are ongoing efforts to develop selective steroid agonists or antagonists of $GABA_A$ receptors as well as selective PR modulators, such as the SPRM, with more tissue- or cell-specific actions. This is obviously an ambitious task but it is not necessarily science-fiction. In fact, much progress in this direction has already been achieved for the estrogens.

Currently, insufficient knowledge of the molecular mechanisms of the actions of progestagens in the nervous system is still hampering the development of more efficient steroid therapies for the injured brain and peripheral nerves. These multiple mechanisms comprise the regulation of gene transcription, the modulation of neurotransmitter receptors, and the activation of signaling cascades via new, recently identified membrane receptors. In particular, the recognition of the significance of nuclear co-regulator proteins in regulating the transcriptional activities of steroid receptors, and the cloning of new membrane steroid receptors, can be expected to completely change our vision of steroid actions on specific target tissues during the next few years.

Because progesterone and its reduced metabolites are strongly upregulated in the damaged and diseased nervous system, stimulating the local synthesis of progesterone may offer novel perspectives, not only for treating lesions of the nervous system but also for neurodegenerative conditions. However, there are still serious gaps in our knowledge of the regulatory mechanisms involved in the biosynthetic pathways of neurosteroids, some of which may be distinct from those described for the steroidogenic endocrine glands. Thus, neuropeptides, neurotransmitters and steroids themselves have been shown to play an important role in the regulation of progesterone formation within the nervous system (Guarneri et al., 1995; Mensah-Nyagan et al., 2001; Micevych et al., 2003; Hojo et al., 2004; Bernardi et al., 2005; Patte-Mensah et al., 2005). Stimulation of pregnenolone synthesis by the activation of NMDA receptors may contribute to increased neurosteroid formation in response to injury, a condition that releases elevated levels of glutamate (Kimoto et al., 2001). A better knowledge of these regulatory circuits would allow a finer control of progesterone synthesis within nervous tissues.

The rapid development of our understanding of progesterone's biosynthesis, mechanisms of action and effects in the nervous system offer very promising possibilities for providing protection to the injured nervous system and promoting regenerative processes. However, more experimental data, and in particular more information about the actions and effects of steroids in injured nervous tissues, are necessary for the development of more targeted and efficient steroid treatments.

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