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Progesterone and progestins: neuroprotection and myelin repair

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Progesterone, known for its role in pregnancy, also exerts marked effects on the nervous system. Its neuroprotective and promyelinating actions, now well documented by experimental studies, make it a particularly promising therapeutic agent for neuroinjury and neurodegenerative diseases. This concept has recently been translated into clinical practice, though there is need for more experimental studies and investigations on the mechanisms of the actions of progesterone. However, it is important to be aware that most of the experimental research concerns the effects of physiological progesterone. Although progesterone represents an interesting therapeutic option, the recognition of its beneficial effects on the nervous system also suggests novel therapeutic benefits for some synthetic progestins derived from progesterone, currently used for contraception or in postmenopausal hormone replacement therapies (HRTs).

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Introduction

The neuroprotective effects of progesterone have received much less attention than those of estradiol, but they are now well documented in a variety of experimental models. In addition, progesterone stimulates the myelination of axons during development and the regeneration of myelin after lesions, also referred to as remyelination or myelin repair [1–3]. To date, two clinical trials have assessed the beneficial effects of progesterone following traumatic brain injury (TBI), and one study is investigating the effects of a synthetic progestin in combination with estradiol in multiple sclerosis (MS). In this review, we will discuss major progress, mainly accomplished over the past two years, concerning our understanding of progesterone as a signal promoting the viability of neurons and the formation of new myelin sheaths. Attention will be drawn to areas that urgently need further exploration, and we shall discuss new therapeutic promises for progestins.

Progesterone signaling: new insights, new challenges

The lack of knowledge concerning the mechanisms underlying the actions of progesterone in the nervous system represents a serious limitation on the development of more efficient and targeted treatments of neurological damage and disorders. Progesterone directly regulates gene expression via two intracellular progesterone receptor (PR) isoforms, PR-A and PR-B [4], but their respective roles in mediating the neuroprotective and promyelinating effects of the hormone have not been explored. The PRs interact as dimers not only with DNA progesterone response elements but also with signaling proteins of the Src/Ras/Erk pathway outside the nucleus [5,6]. The recent identification of membrane receptors of progesterone, unrelated to the intracellular receptors, provides opportunities for the development of new cell membrane-specific progestin ligands [7,8] (Figure 1). However, we are ignorant of the biological significance of these new receptors in the nervous system. Major effects of progesterone on neurons and glial cells are mediated by its metabolite allopregnanolone (3α,5α-tetrahydroprogesterone), which is a potent positive modulator of γ-aminobutyric acid type A ($GABA_A$) receptors [9••]. Recently, the antagonism of sigma-1 (σ1) receptors by progesterone has been shown to be involved in acute neuroprotection after ischemic brain damage [10].

Progestagens: controversial terminology and misconceptions

The different use of the terms progesterone, progestins, and progestagens continues to create considerable confusion. Progesterone only refers to the physiological hormone and should never be used as a generic term for progestins [11•]. The term 'progestin' is not used in a consistent manner, and we propose to use it exclusively to designate synthetic compounds. The term 'progestagen' (or progestogen) is a functional definition and refers to steroids that possess progestational activity, including both progesterone and the synthetic progestins.

The progestins belong to different classes and are related either to testosterone or to progesterone [12] (Figure 2). It is important to be aware that very small structural changes result in considerable differences in their pharmacological properties and actions. Among the most selective and

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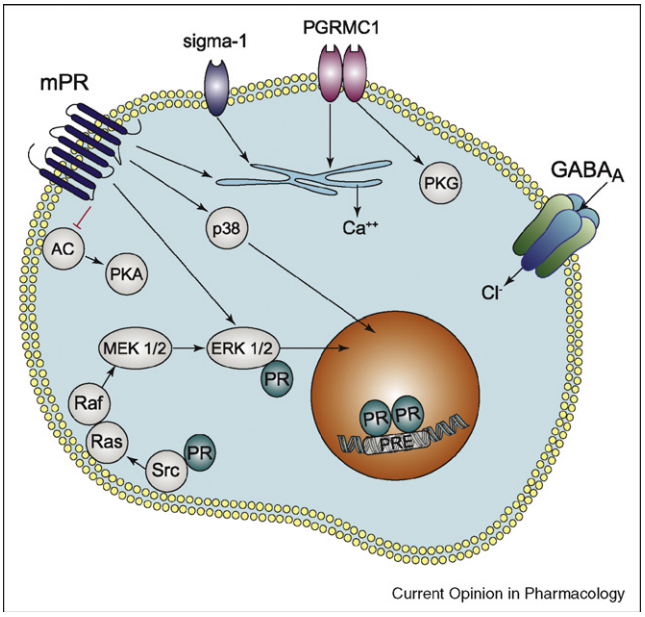
Figure 1



The multiple mechanisms of progesterone signaling not only raise challenges but also offer new opportunities for neuroprotection and myelin repair. Progesterone regulates gene transcription by binding to intracellular receptors (PRs), which interact as dimers with DNA progesterone response elements (PREs). In addition, PR can also directly interact with extranuclear signaling proteins of the Src/Ras/Erk pathway. At the level of the plasma membrane, progesterone binds to the recently identified membrane receptors of progesterone (mPR, comprising the α, β, and γ isoforms), progesterone receptor membrane component 1 (PGRMC1, the former protein 25Dx) and the σ1 receptor. Major signal transduction pathways which have been shown to be activated by the mPRs are ERK and p38. The mPRs also inhibit the adenylate cyclase (AC), and as a consequence the protein kinase A (PKA) pathway, and they stimulate Ca^{2+} release from internal stores. Likewise, PGRMC1 and σ1 receptors increase intracellular Ca^{2+} release. Both receptors are also located on membranes inside the cytoplasm, but they may translocate from them to the plasma membrane. In addition, PGRMC1 has been shown to activate protein kinase G (PKG), and σ1 receptors function as amplifiers of ion channels (e.g. voltage-gated K^+ channels) and neurotransmitter receptors (e.g. NMDA receptors). Progesterone also activates $GABA_A$ receptors via its metabolite allopregnanolone.

potent PR agonists are the 19-norprogesterone derivatives [13]. On the contrary, medroxyprogesterone acetate (MPA) also binds to other steroid receptors and has deleterious effects on neurons [2]. Very little is known concerning the *in situ* metabolism of progestins and the actions of their metabolites, in particular on $GABA_A$ receptors, though according to the steroid structure their administration can affect brain levels of allopregnanolone [14]. Another important point is that progestins have been designed to target the classical intracellular PRs, and several of them have very little or no affinity for membrane progesterone receptors (mPRs) [15•]. Thus, progestins do not mimic all the biological effects of progesterone, but this does not preclude their utility for the specific targeting of PR-dependent neuroprotective mechanisms.

Progesterone as a neuroprotective agent

A systematic meta-analysis of experimental studies has confirmed that progesterone treatment is efficient in reducing the lesion volume following cerebral ischemia or TBI [16]. Importantly, progesterone inhibits ischemic brain injury after either transient or permanent occlusion of brain arteries, the latter being a common case of human stroke [17]. One of the best-studied brain injury models is focal contusion lesion of the rat prefrontal cortex. In this model, progesterone treatment significantly reduces secondary neuronal death, edema, and inflammation and improves functional recovery in males, females being protected by their elevated endogenous levels of the hormone [3]. These important findings have now been extended to diffuse TBI, representative of common clinical head injuries [18].

The neuroprotective effects of progesterone have been extensively studied in the rat spinal cord, either after injury or in the Wobbler mouse, a model of spontaneous motoneuron degeneration [19]. The marked protective effects of progesterone on spinal motoneurons involve upregulation of brain-derived neurotrophic factor (BDNF), a key regulator of neuronal and glial functions [20]. These studies have provided the basis for an important concept: genes, which otherwise do not respond to progesterone, become hormone-sensitive after injury or in neurodegenerative conditions. Neuroprotective effects of progesterone have also been observed in other models of neurological disorders [21,22].

Although steroids are part of complex hormonal signaling networks, laboratories are often specialized in the study of a single type of hormone. The interactions between progesterone and estradiol in neuroprotective mechanisms have only begun to be explored, and the first results reveal their complexity. Thus, in the triple transgenic mouse model of Alzheimer's disease (AD)-like neuropathology (3xTgAD mice), progesterone blocked the beneficial effects of estradiol on β-amyloid accumulation, but not on hippocampal-dependent behavioral impairments. However, whether administered alone or in combination with estradiol, progesterone significantly reduced tau hyperphosphorylation [23•]. Progesterone and estradiol also enhanced the functional efficiency of brain mitochondria, but again, the response magnitude was decreased when they were administered together [24].

The progesterone metabolite allopregnanolone plays an important role in neuroprotection, though its precise role still needs to be defined. Thus, after TBI or transient occlusion of brain arteries, allopregnanolone showed great efficiency in providing neuroprotection [3]. In the above-mentioned triple transgenic mouse model of AD, allopregnanolone had beneficial effects on disease markers, reversed cognitive deficits and stimulated neurogenesis [25]. In a mouse model of Niemann–Pick C disease, an

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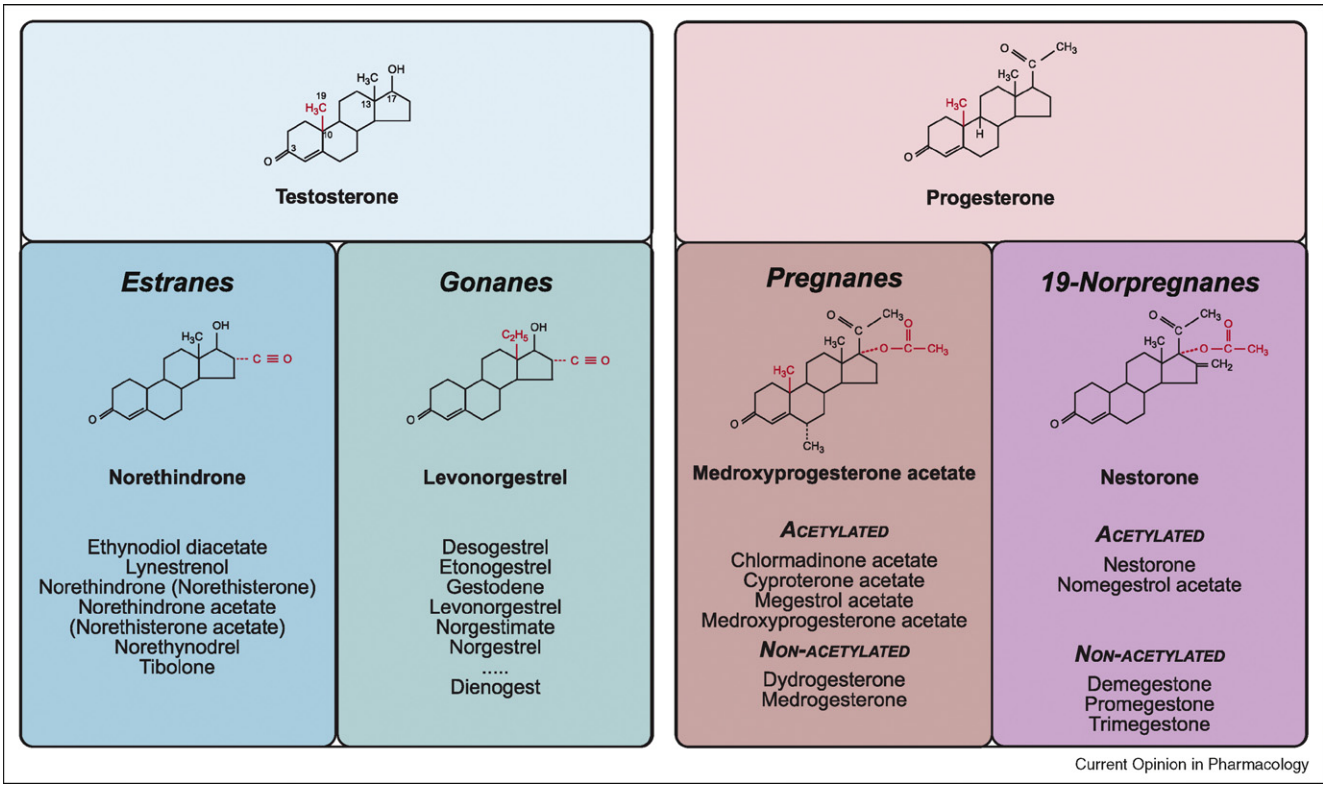
Figure 2



A classification for progestins according to their chemical structures. Progestins are structurally related either to testosterone or to progesterone. For most progestins related to testosterone, carbon 19 has been removed (19-nortestosterone derivatives), conferring progestational activity to the molecules, and an ethinyl group has been added to C17, resulting in orally active substances. They can be subdivided into the estranes (a methyl group at C13) and the gonanes (an ethyl group at C13, except for dienogest). Progestins related to progesterone can be subdivided into pregnanes, with a methyl group at C10, and 19-norpregnanes, devoid of this group (no radical in position C19). Both pregnanes and 19-norpregnanes have either an acetate group at C17 or are not acetylated. The most recent progestins, including nestorone, nomegestrol acetate, dienogest, and trimegestone, have been designed to selectively target the PRs. Other types of progestins have been recently designed, like drospirenone, which is derived from the aldosterone antagonist spirolactone and has antimineralocorticoid and antiandrogenic properties.

earlier study has shown that the neonatal administration of allopregnanolone increases the survival of cerebellar neurons and doubles the lifespan of the animals [26•].

Progesterone as a promyelinating agent

Compared to recent studies on the neuroprotective effects of progesterone, investigations of its role in myelination have been more sparse. Hormone effects on myelination deserve more attention: first, the viability of neurons is dependent on myelin-forming glial cells, oligodendrocytes in the central nervous system (CNS), and Schwann cells in the peripheral nervous system (PNS) [27]; second, demyelination of axons is a major contributor to the loss of function following traumatic injuries [28]; third, prompt myelin repair protects axons from degeneration [29].

One of the most frequent neurological disorders, MS, is characterized by focal myelin destruction, axonal pathology, and neurological dysfunction. The corresponding disease model, experimental autoimmune encephalitis (EAE), can be induced by injecting immunodominant peptides from myelin proteins into mice. It is well established that the administration of estradiol before EAE induction reduces pathological symptoms and provides neuroprotection [30,31]. Beneficial effects of progesterone on EAE outcome have now been demonstrated. Treating mice with progesterone starting one week before EAE induction reduced the infiltration of inflammatory cells and demyelination in the spinal cord, normalized the expression of neuronal proteins, and improved the clinical scores [32•]. In addition, progesterone may have a beneficial influence on myelin repair, a spontaneous regenerative response mediated by an endogenous population of oligodendrocyte precursor cells (OPCs) [33]. In response to a lesion, OPC proliferate, migrate to the demyelinated axons, and differentiate into myelinating oligodendrocytes. Earlier studies had shown that progesterone increases the proliferation of OPC [34,35]. The recent observation that progesterone also promotes the differentiation of OPC into oligodendrocytes after spinal cord injury points to a key role for the hormone in this process [36].

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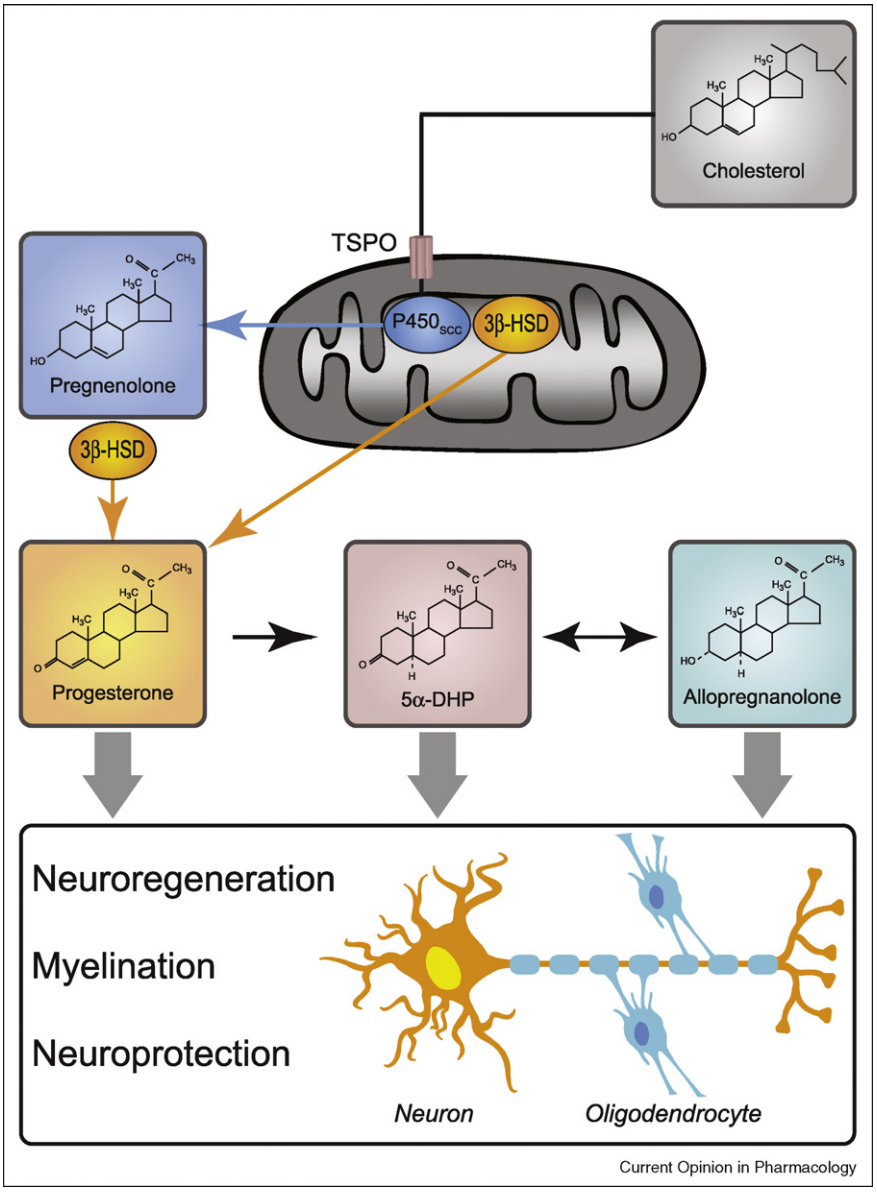
A role of progesterone in myelination was first demonstrated in the regenerating mouse sciatic nerve and in explant cultures of dorsal root ganglia (DRG) [37]. More recent studies have also provided evidence for a role of allopregnanolone in peripheral nerve myelination [38]. From these observations, it is tempting to draw the conclusion that progesterone may always be beneficial for peripheral nerve regeneration. Instead, it may have adverse effects in certain peripheral neuropathies, such as Charcot-Marie-Tooth disease type 1A (CMT1A), caused by overexpression of the 22-kDa peripheral myelin protein PMP22 [39]. Already 10 years ago, it was shown that progesterone stimulates *PMP22* promoter activity, and could thus be expected to negatively affect CMT1A by further increasing the PMP22 dosage [40]. The proof for this concept has been provided by studying the effects of progesterone and of an antiprogestin in a transgenic rat model of CMT1A [41]. The same group has now shown

Figure 3



Cholesterol is converted to pregnenolone by cytochrome P450scc inside steroidogenic mitochondria. The transport of cholesterol across the mitochondrial membranes is a limiting step, and it involves the transport protein TSPO. Ligands of TSPO can stimulate the passage of cholesterol into the mitochondria and, as a consequence, the synthesis of pregnenolone. The conversion of pregnenolone to progesterone by different isoforms of the 3β-hydroxysteroid dehydrogenase (3β-HSD) also takes place inside the mitochondria or within the cytoplasm. Progesterone synthesized by neurons and glial cells plays an important role in neuroprotection and myelination.

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that long-term antiprogestin treatment of CMTA1 rats can prevent axon loss in the absence of a beneficial influence on myelin [42•].

Progesterone as a neurosteroid

Progesterone present in nervous tissues is in part derived from the steroidogenic endocrine glands, but it is also synthesized *de novo* from cholesterol by neurons and glial cells, and in this case qualifies as a 'neurosteroid' [43]. There are three major arguments in support of the synthesis of progesterone within the nervous system: first, the presence and activity of the enzymes necessary for its biosynthesis; second, its persistence in the absence of the steroidogenic endocrine glands; third, the stimulation of its local synthesis by ligands of the translocator protein (18 kDa) (TSPO; the former peripheral benzodiazepine receptor or PBR) [1] (Figure 3).

The physiopathological significance of progesterone synthesis within the CNS and PNS remains an important question. During development, neuronal progesterone plays an important role in dendritic growth and synaptogenesis as revealed by the study of Purkinje cells [44]. In the adult CNS, progesterone is upregulated in response to injury, inflammation, neuropathic pain, and pathological conditions such as diabetes [45,46]. These observations suggest important functions for locally synthesized progesterone in promoting neuronal survival, regulating neuroinflammation, and controlling pain thresholds. Synthesis of progesterone in the brain also plays an important role in the regulation of reproductive functions, previously thought to be exclusively under the control of ovarian hormones [47].

Electrophysiological studies have provided compelling evidence for the importance of locally synthesized allopregnanolone in controlling neuronal activity via the modulation of $GABA_A$ receptors. To fully understand the implications of these studies, it is important to be aware of a recent breakthrough in our understanding of $GABA_A$ receptor-mediated inhibition, which involves not only the rapid and phasic activation of $GABA_A$ receptors located at synaptic contacts but also the persistent tonic activation of specific subtypes of extra-synaptic $GABA_A$ receptors [48]. The latter have emerged as major targets for the actions of allopregnanolone in spinal dorsal horns [49••]. Most importantly, miniature inhibitory postsynaptic currents (mIPSCs) in the dorsal horns are tonically facilitated by locally produced allopregnanolone in a lamina-specific manner during early postnatal life. In more mature animals, local allopregnanolone synthesis is reactivated by peripheral inflammation [50••].

From experimental studies to therapeutic targeting

Experimental studies thus offer promises for progesterone treatment of injuries and disorders of the nervous system. Two clinical trials have assessed the protective effect of progesterone after TBI. In a first phase II trial, patients received state-of-the-art emergency treatment within 11 hours of TBI plus three days of intravenous progesterone or vehicle. At 30 days postinjury, progesterone was found to have reduced mortality in severely injured patients and to have improved functional outcome in patients with moderate TBI [51•]. The aim of the second clinical study was to analyze the longer term efficacy of progesterone on neurologic outcome in TBI patients. Within eight hours of injury, they received intramuscular injections of progesterone or placebo for five consecutive days. Patients in the progesterone group had improved neurological scores, and their mortality rate was significantly lower at six-month follow-up [52]. In 2005, a placebo-controlled clinical trial aimed at preventing MS relapses related to the postpartum condition by nomegestrol acetate (a 19-norprogesterone derivative) in combination with estradiol was launched [53].

Conclusions

Progesterone and progestins as a class of steroids have gained a bad reputation due to the negative outcomes of recent HRT trials conducted with MPA, and it has been proposed to omit them from treatments [11•]. However, experimental studies have demonstrated the multiple beneficial actions of progesterone and its derivatives in the nervous system, and there is now clinical evidence for the safety of physiological progesterone. Thus, the time has come to change our way of thinking, and the idea of using progesterone in neurological practice is making its way. Progesterone is indeed an excellent candidate molecule for neuroprotection and myelin repair, because it easily crosses the blood–brain barrier and exerts concerted beneficial influences on multiple processes. The finding that progesterone is locally produced within the nervous system opens perspectives for an additional therapeutic strategy. The idea is to increase the local synthesis of endogenous progesterone by TSPO drug ligands. However, conclusive experimental evidence for the role of locally synthesized progesterone in neuroprotection and neuroregeneration remains to be established.

Although physiological progesterone represents an interesting therapeutic option for treating lesions and disease of the nervous system, progestins derived from progesterone with selective actions on the classical PR, such as those related to 19-norprogesterone, offer interesting promises for PR-dependent neuroprotective mechanisms. Negative effects associated with some progestins should indeed not be generalized to the entire class. New therapeutic targets for progesterone are provided by the discovery of the membrane receptors. However, much remains to be learned concerning the significance of the different progesterone-signaling mechanisms and the actions of different progestins inside the nervous system.

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- •• of outstanding interest

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