

TOPIC: progesterone exert neuroprotective and myelinating effects on the nervous system

1: [Ann Emerg Med. 2008 Feb;51\(2\):164-72. Epub 2007 Jun 22.](#)

Does progesterone have neuroprotective properties?

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In this article, we review published preclinical and epidemiologic studies that examine progesterone's role in the central nervous system. Its effects on the reproductive and endocrine systems are well known, but a large and growing body of evidence, including a recently published pilot clinical trial, indicates that the hormone also exerts neuroprotective effects on the central nervous system. We now know that it is produced in the brain, for the brain, by neurons and glial cells in the central and peripheral nervous system of both male and female individuals. Laboratories around the world have reported that administering relatively large doses of progesterone during the first few hours to days after injury significantly limits central nervous system damage, reduces loss of neural tissue, and improves functional recovery. Although the research published to date has focused primarily on progesterone's effects on blunt traumatic brain injury, there is evidence that the hormone affords protection from several forms of acute central nervous system injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury. Progesterone appears to exert its protective effects by protecting or rebuilding the blood-brain barrier, decreasing development of cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis. All are plausible mechanisms of neuroprotection.

1: [Brain Res Rev. 2008 Mar;57\(2\):386-97. Epub 2007 Jul 27.](#)

Progesterone exerts neuroprotective effects after brain injury.

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Progesterone, although still widely considered primarily a gender hormone, is an important agent affecting many central nervous system functions. This review assesses recent, primarily in vivo, evidence that progesterone can play an important role in promoting and enhancing repair after traumatic brain injury and stroke. Although many of its specific actions on neuroplasticity remain to be discovered, there is growing evidence that this hormone may be a safe and effective treatment for traumatic brain injury and other neural disorders in humans.

1: [Neuroscience. 2008 Aug 26;155\(3\):673-85. Epub 2008 Jun 19.](#)

Neuroprotective effects of dihydroprogesterone and progesterone in an experimental model of nerve crush injury.

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A satisfactory management to ensure a full restoration of peripheral nerve after trauma is not yet available. Using an experimental protocol, in which crush injury was applied 1 cm above the bifurcation of the rat sciatic nerve for 20 s, we here demonstrate that the levels of neuroactive steroids, such as pregnenolone and progesterone (P) metabolites (i.e. dihydroprogesterone, DHP, and tetrahydroprogesterone, THP) present in injured sciatic nerve were significantly decreased. On this basis, we have focused our attention on DHP and its direct precursor, P, analyzing whether these two neuroactive steroids may have neuroprotective effects on biochemical, functional and morphological alterations occurring during crush-induced degeneration-regeneration. We demonstrate that DHP and/or P counteract biochemical

alterations (i.e. myelin proteins and Na(+),K(+)-ATPase pump) and stimulate reelin gene expression. These two neuroactive steroids also counteract nociception impairment, and DHP treatment significantly decreases the up-regulation of myelinated fibers' density occurring in crushed animals. **Altogether, these observations suggest that DHP and P (i.e. two neuroactive steroids interacting with progesterone receptor) may be considered protective agents in case of nerve crush injury.**

1: *Glia*. 2008 Dec 2. [Epub ahead of print]

Effects of progesterone on oligodendrocyte progenitors, oligodendrocyte transcription factors, and myelin proteins following spinal cord injury.

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Progesterone is emerging as a myelinizing factor for central nervous system injury. Successful remyelination requires proliferation and differentiation of oligodendrocyte precursor cells (OPC) into myelinating oligodendrocytes, but this process is incomplete following injury. To study progesterone actions on remyelination, we administered progesterone (16 mg/kg/day) to rats with complete spinal cord injury. Rats were euthanized 3 or 21 days after steroid treatment. Short progesterone treatment (a) increased the number of OPC without effect on the injury-induced reduction of mature oligodendrocytes, (b) increased mRNA and protein expression for the myelin basic protein (MBP) without effects on proteolipid protein (PLP) or myelin oligodendrocyte glycoprotein (MOG), and (c) increased the mRNA for Olig2 and Nkx2.2 transcription factors involved in specification and differentiation of the oligodendrocyte lineage. Furthermore, long progesterone treatment (a) reduced OPC with a concomitant increase of oligodendrocytes; (b) promoted differentiation of cells that incorporated bromodeoxyuridine, early after injury, into mature oligodendrocytes; (c) increased mRNA and protein expression of PLP without effects on MBP or MOG; and (d) increased mRNA for the Olig1 transcription factor involved in myelin repair. **These results suggest that early progesterone treatment enhanced the density of OPC and induced their differentiation into mature oligodendrocytes by increasing the expression of Olig2 and Nkx2.2. Twenty-one days after injury, progesterone favors remyelination by increasing Olig1 (involved in repair of demyelinated lesions), PLP expression, and enhancing oligodendrocytes maturation. Thus, progesterone effects on oligodendrogenesis and myelin proteins may constitute fundamental steps for repairing traumatic injury inflicted to the spinal cord. (c) 2008 Wiley-Liss, Inc.**

1: *J Mol Neurosci*. 2006;28(1):3-15.

Progesterone treatment of spinal cord injury: Effects on receptors, neurotrophins, and myelination.

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In addition to its traditional role in reproduction, progesterone (PROG) has demonstrated neuroprotective and promyelinating effects in lesions of the peripheral and central nervous systems, including the spinal cord. The latter is a target of PROG, as nuclear receptors, as well as membrane receptors, are expressed by neurons and/or glial cells. When spinal cord injury (SCI) is produced at the thoracic level, several genes become sensitive to PROG in the region caudal to the lesion site. Although the cellular machinery implicated in PROG neuroprotection is only emerging, neurotrophins, their receptors, and signaling cascades might be part of the molecules involved in this process. In rats with SCI, a 3-d course of PROG treatment increased the mRNA of brain-derived neurotrophic factor (BDNF) and BDNF immunoreactivity in perikaryon and processes of motoneurons, whereas chromatolysis was strongly prevented. The increased expression of BDNF correlated with increased immunoreactivity for the BDNF receptor TrkB and for phosphorylated cAMP-responsive element binding in motoneurons. In the same SCI model, PROG restored myelination, according to measurements of myelin basic protein (MBP) and mRNA levels, and further increased the density of NG2+-positive oligodendrocyte progenitors. These cells might be involved in remyelination of the lesioned

spinal cord. Interestingly, similarities in the regulation of molecular parameters and some cellular events attributed to PROG and BDNF (i.e., choline acetyltransferase, Na,K-ATPase, MBP, chromatolysis) suggest that BDNF and PROG might share intracellular pathways. Furthermore, PROG-induced BDNF might regulate, in a paracrine or autocrine fashion, the function of neurons and glial cells and prevent the generation of damage.

1: [Brain Res. 2008 May 7;1208:17-24. Epub 2008 Mar 6.](#)

Transdifferentiation of bone marrow stromal cells into Schwann cell phenotype using progesterone as inducer.

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Bone marrow stromal cells (BMSCs) were reported to transdifferentiate into Schwann cells by a two-stage protocol, using beta-mercaptoethanol and retinoic acid (BME-RA) as preinducers (preinduction stage: PS) and platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), forskolin (FSK) and heregulin (HRG) as inducers (induction stage: IS). In this study, six groups were used, group one was used as control (PS: BME-RA; IS: PDGF, bFGF, FSK and HRG). In group 2, the preinducer was similar to group 1, and in the induction stage, progesterone replaced HRG. In groups 3 and 4, the preinducer was progesterone; and at the induction stage, the inducer was similar to groups 1 and 2. Accordingly, in groups 5 and 6, the preinducer was FSK. The immunohistochemical differentiation markers were S-100 and P0, and RT-PCR markers were OCT-4 and P0 at the preinduction stage, while at the induction stage P0 and NeuroD were used. The results of the study showed that S-100 was expressed in the groups after the induction stage, however, P0 was not expressed in any group. There was not any significant difference between the percentage of S100 positive cells in the 1st and 2nd groups. P0 was expressed at the mRNA level in the undifferentiated BMSCs and in the 3rd and 4th groups after the preinduction and the induction stages. **The conclusion of this study is that progesterone can induce BMSCs into Schwann cell phenotype.**

1: [J Steroid Biochem Mol Biol. 2007 Nov-Dec;107\(3-5\):228-37. Epub 2007 Jun 22.](#)

Effects of progesterone in the spinal cord of a mouse model of multiple sclerosis.

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The spinal cord is a target of progesterone (PROG), as demonstrated by the expression of intracellular and membrane PROG receptors and by its myelinating and neuroprotective effects in trauma and neurodegeneration. Here we studied PROG effects in mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis characterized by demyelination and immune cell infiltration in the spinal cord. Female C57BL/6 mice were immunized with a myelin oligodendrocyte glycoprotein peptide (MOG(40-54)). One week before EAE induction, mice received single pellets of PROG weighing either 20 or 100 mg or remained free of steroid treatment. On average, mice developed clinical signs of EAE 9-10 days following MOG administration. The spinal cord white matter of EAE mice showed inflammatory cell infiltration and circumscribed demyelinating areas, demonstrated by reductions of luxol fast blue (LFB) staining, myelin basic protein (MBP) and proteolipid protein (PLP) immunoreactivity (IR) and PLP mRNA expression. In motoneurons, EAE reduced the expression of the alpha 3 subunit of Na,K-ATPase mRNA. In contrast, EAE mice receiving PROG showed less inflammatory cell infiltration, recovery of myelin proteins and normal grain density of neuronal Na,K-ATPase mRNA. Clinically, PROG produced a moderate delay of disease onset and reduced the clinical scores. Thus, PROG attenuated disease severity, and reduced the inflammatory response and the occurrence of demyelination in the spinal cord during the acute phase of EAE.

1: [Pharmacol Ther. 2007 Oct;116\(1\):77-106. Epub 2007 Jun 18.](#)

Progesterone: therapeutic opportunities for neuroprotection and myelin repair.

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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.

1: *Growth Horm IGF Res.* 2004 Jun;14 Suppl A:S18-33.

Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination.

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Progesterone (PROG) is synthesized in the brain, spinal cord and peripheral nerves. Its direct precursor pregnenolone is either derived from the circulation or from local de novo synthesis as cytochrome P450_{scc}, which converts cholesterol to pregnenolone, is expressed in the nervous system. Pregnenolone is converted to PROG by 3β-hydroxysteroid dehydrogenase (3β-HSD). In situ hybridization studies have shown that this enzyme is expressed throughout the rat brain, spinal cord and dorsal root ganglia (DRG) mainly by neurons. Macroglial cells, including astrocytes, oligodendroglial cells and Schwann cells, also have the capacity to synthesize PROG, but expression and activity of 3β-HSD in these cells are regulated by cellular interactions. Thus, Schwann cells convert pregnenolone to PROG in response to a neuronal signal. There is now strong evidence that P450_{scc} and 3β-HSD are expressed in the human nervous system, where PROG synthesis also takes place. Although there are only a few studies addressing the biological significance of PROG synthesis in the brain, the autocrine/paracrine actions of locally synthesized PROG are likely to play an important role in the viability of neurons and in the formation of myelin sheaths. The neuroprotective effects of PROG have recently been documented in a murine model of spinal cord motoneuron degeneration, the Wobbler mouse. The treatment of symptomatic Wobbler mice with PROG for 15 days attenuated the neuropathological changes in spinal motoneurons and had beneficial effects on muscle strength and the survival rate of the animals. PROG may exert its neuroprotective effects by regulating expression of specific genes in neurons and glial cells, which may become hormone-sensitive after injury. The promyelinating effects of PROG were first documented in the mouse sciatic nerve and in co-cultures of sensory neurons and Schwann cells. PROG also promotes myelination in the brain, as shown in vitro in explant cultures of cerebellar slices and in vivo in the cerebellar peduncle of aged rats after toxin-induced demyelination. Local synthesis of PROG in the brain and the neuroprotective and promyelinating effects of this neurosteroid offer interesting therapeutic possibilities for the prevention and treatment of neurodegenerative diseases, for accelerating regenerative processes and for preserving cognitive functions during aging.

1: *Neuroscience.* 2004;125(3):605-14.

Progesterone up-regulates neuronal brain-derived neurotrophic factor expression in the injured spinal cord.

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Progesterone (PROG) provides neuroprotection to the injured central and peripheral nervous system. These effects may be due to regulation of myelin synthesis in glial cells and also to direct actions on neuronal function. Recent studies point to neurotrophins as possible mediators of hormone action. Here, we show that the expression of brain-derived neurotrophic factor (BDNF) at both the mRNA and protein levels was increased by PROG treatment in ventral horn motoneurons from rats with spinal cord injury (SCI). Semiquantitative *in situ* hybridization revealed that SCI reduced BDNF mRNA levels by 50% in spinal motoneurons (control: 53.5±7.5 grains/mm² vs. SCI: 27.5±1.2, $P<0.05$), while PROG administration to injured rats (4 mg/kg/day during 3 days, *s.c.*) elicited a three-fold increase in grain density (SCI+PROG: 77.8±8.3 grains/mm², $P<0.001$ vs. SCI). In addition, PROG enhanced BDNF immunoreactivity in motoneurons of the lesioned spinal cord. Analysis of the frequency distribution of immunoreactive densities (χ^2 : 812.73, $P<0.0001$) showed that 70% of SCI+PROG motoneurons scored as dark stained whereas only 6% of neurons in the SCI group belonged to this density score category ($P<0.001$). PROG also prevented the lesion-induced chromatolytic degeneration of spinal cord motoneurons as determined by Nissl staining. In the normal intact spinal cord, PROG significantly increased BDNF immunoreactivity in ventral horn neurons, without changes in mRNA levels. Our findings suggest that PROG enhancement of endogenous neuronal BDNF could provide a trophic environment within the lesioned spinal cord and might be part of the PROG activated-pathways to provide neuroprotection.

1: [Neuroscience. 2007 Feb 23;144\(4\):1293-304. Epub 2006 Dec 20.](#)

Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: a multimodal analysis.

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One important complication of diabetes is damage to the peripheral nervous system. However, in spite of the number of studies on human and experimental diabetic neuropathy, the current therapeutic arsenal is meagre. Consequently, the search for substances to protect the nervous system from the degenerative effects of diabetes has high priority in biomedical research. Neuroactive steroids might be interesting since they have been recently identified as promising neuroprotective agents in several models of neurodegeneration. We have assessed whether chronic treatment with progesterone (P), dihydroprogesterone (DHP) or tetrahydroprogesterone (THP) had neuroprotective effects against streptozotocin (STZ)-induced diabetic neuropathy at the neurophysiological, functional, biochemical and neuropathological levels. Using gas chromatography coupled to mass-spectrometry, we found that three months of diabetes markedly lowered P plasma levels in male rats, and chronic treatment with P restored them, with protective effects on peripheral nerves. In the model of STZ-induced diabetic neuropathy, chronic treatment for 1 month with P, or with its derivatives, DHP and THP, counteracted the impairment of nerve conduction velocity (NCV) and thermal threshold, restored skin innervation density, and improved Na(+),K(+)-ATPase activity and mRNA levels of myelin proteins, such as glycoprotein zero and peripheral myelin protein 22, suggesting that these neuroactive steroids, might be useful protective agents in diabetic neuropathy. Interestingly, different receptors seem to be involved in these effects. Thus, while the expression of myelin proteins and Na(+),K(+)-ATPase activity are only stimulated by P and DHP (i.e. two neuroactive steroids interacting with P receptor, PR), NCV, thermal nociceptive threshold and intra-epidermal nerve fiber (IENF) density are also affected by THP, which interacts with GABA-A receptor. Because, a therapeutic approach with specific synthetic receptor ligands could avoid the typical side effects of steroids, future experiments will be devoted to evaluating the role of PR and GABA-A receptor in these protective effects.

1: [J Mol Neurosci. 2006;28\(1\):65-76.](#)

Neuroactive steroids: A therapeutic approach to maintain peripheral nerve integrity during neurodegenerative events.

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It is now well known that peripheral nerves are a target for the action of neuroactive steroids. This review summarizes observations obtained so far, indicating that through the interaction with classical and nonclassical steroid receptors, neuroactive steroids (e.g., progesterone, testosterone and their derivatives, estrogens, etc.) are able to influence several parameters of the peripheral nervous system, particularly its glial compartment (i.e., Schwann cells).

Interestingly, some of these neuroactive steroids might be considered as promising neuroprotective agents. They are able to counteract neurodegenerative events of rat peripheral nerves occurring after experimental physical trauma, during the aging process, or in hereditary demyelinating diseases. On this basis, the hypothesis that neuroactive steroids might represent a new therapeutic strategy for peripheral neuropathy is proposed.

1: *Neurosci Lett.* 2006 Jul 10;402(1-2):150-3. Epub 2006 Apr 19.

Neuroactive steroids prevent peripheral myelin alterations induced by diabetes.

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The effect of the neuroactive steroids progesterone, dihydroprogesterone and tetrahydroprogesterone on myelin abnormalities induced by diabetes was studied in the sciatic nerve of adult male rats treated with streptozotocin. Streptozotocin increased blood glucose levels and decreased body weight gain, parameters not affected by steroids. Streptozotocin increased the number of fibers with myelin infoldings in the axoplasm, 8 months after the treatment.. Chronic treatment for 1 month with progesterone and dihydroprogesterone resulted in a significant reduction in the number of fibers with myelin infoldings to control levels. Treatment with tetrahydroprogesterone did not significantly affect this myelin alteration. These results suggest that neuroactive steroids such as progesterone and dihydroprogesterone may represent therapeutic alternatives to counteract peripheral myelin alterations induced by diabetes.

1: *Growth Horm IGF Res.* 2004 Jun;14 Suppl A:S18-33.

Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination.

Schumacher M, Guennoun R, Robert F, Carelli C, Gago N, Ghomari A, Gonzalez Deniselle MC, Gonzalez SL, Ibanez C, Labombarda F, Coirini H, Baulieu EE, De Nicola AF.

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Progesterone (PROG) is synthesized in the brain, spinal cord and peripheral nerves. Its direct precursor pregnenolone is either derived from the circulation or from local de novo synthesis as cytochrome P450scc, which converts cholesterol to pregnenolone, is expressed in the nervous system. Pregnenolone is converted to PROG by 3beta-hydroxysteroid dehydrogenase (3beta-HSD). In situ hybridization studies have shown that this enzyme is expressed throughout the rat brain, spinal cord and dorsal root ganglia (DRG) mainly by neurons. Macroglial cells, including astrocytes, oligodendroglial cells and Schwann cells, also have the capacity to synthesize PROG, but expression and activity of 3beta-HSD in these cells are regulated by cellular interactions. Thus, Schwann cells convert pregnenolone to PROG in response to a neuronal signal. There is now strong evidence that P450scc and 3beta-HSD are expressed in the human nervous system, where PROG synthesis also takes place. Although there are only a few studies addressing the biological significance of PROG synthesis in the brain, the autocrine/paracrine actions of locally synthesized PROG are likely to play an important role in the viability of neurons and in the formation of myelin sheaths. The neuroprotective effects of PROG have recently been documented in a murine model of spinal cord motoneuron degeneration, the Wobbler mouse. The treatment of symptomatic Wobbler mice with PROG for 15 days attenuated the

neuropathological changes in spinal motoneurons and had beneficial effects on muscle strength and the survival rate of the animals. PROG may exert its neuroprotective effects by regulating expression of specific genes in neurons and glial cells, which may become hormone-sensitive after injury. The promyelinating effects of PROG were first documented in the mouse sciatic nerve and in co-cultures of sensory neurons and Schwann cells.. PROG also promotes myelination in the brain, as shown in vitro in explant cultures of cerebellar slices and in vivo in the cerebellar peduncle of aged rats after toxin-induced demyelination. Local synthesis of PROG in the brain and the neuroprotective and promyelinating effects of this neurosteroid offer interesting therapeutic possibilities for the prevention and treatment of neurodegenerative diseases, for accelerating regenerative processes and for preserving cognitive functions during aging.

1: [Steroids. 2000 Oct-Nov;65\(10-11\):605-12.](#)

Comment in:

[Hum Reprod. 2001 Aug;16\(8\):1542.](#)

Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination.

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Some steroids are synthesized within the central and peripheral nervous system, mostly by glial cells. These are known as neurosteroids. In the brain, certain neurosteroids have been shown to act directly on membrane receptors for neurotransmitters. For example, progesterone inhibits the neuronal nicotinic acetylcholine receptor, whereas its 3alpha,5alpha-reduced metabolite 3alpha, 5alpha-tetrahydroprogesterone (allopregnanolone) activates the type A gamma-aminobutyric acid receptor complex. Besides these effects, neurosteroids also regulate important glial functions, such as the synthesis of myelin proteins. Thus, in cultures of glial cells prepared from neonatal rat brain, progesterone increases the number of oligodendrocytes expressing the myelin basic protein (MBP) and the 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase). An important role for neurosteroids in myelin repair has been demonstrated in the rodent sciatic nerve, where progesterone and its direct precursor pregnenolone are synthesized by Schwann cells. **After cryolesion of the male mouse sciatic nerve, blocking the local synthesis or action of progesterone impairs remyelination of the regenerating axons, whereas administration of progesterone to the lesion site promotes the formation of new myelin sheaths.**