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Progesterone and neuroprotection at menopause

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Abstract

The neuroprotective effect of progesterone has been demonstrated in numerous experimental cell and animal studies, in traumatic brain/spinal injury, neurodegenerative diseases, storke, demyelinating diseases. Thus progesterone has emerged as a promising candidate for preventing and treating neuronal related disorders leading to a few promising clinical studies.The effects of progesterone in the nervous system involve a variety of signaling actions, therefore we review the evidence that supports the neuroprotective effects of progesterone and recall the mechanisms that mediate these effects. We also discuss the biology of progesterone and the effects of this hormone on myelination and remyelination of the central and peripheral nervous system. Progesterone in the brain is derived from the steroidogenic endocrine glands or from local synthesis by neural cells. Stimulating the formation of endogenous progesterone is currently explored as an alternative strategy for neuroprotection, axonal regeneration, and myelin repair.
Keywords: *progesterone, neuroprotection, pregesterone receptor, progestins, traumatic brain injury, neurodegenerative diseases*

Introduction

Considering the life expectancy rise, the postmenopausal population is growing and the health related decisions this women will need to consider if the use of hormone therapy not just for managing postmenopausal symptoms but potentially for neuroprotection to help maintain a healthy brain[(1)].

Progesterone is a major gonadal hormone synthesized in the female body primarily by the corpus lutheum of the ovary during the lutheal phase of the menstrual cycle but also by the adrenal glands, where its synthesis is under the control of adrenocorticotropic hormone (ACTH). However, this hormone may also be synthesized de novo within the nervous system, both central and peripheral, which makes it a neurosteroid. The fact that it is produced by glial cells (oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS)) made scientists wonder if progesterone may have other functions beyond the reproductive ones. Therefore over the past two decades the interest in progesterone's neurological effects has increased, leading to multiple research studies that have proven its neuroprotective and neuromodulatory functions[(2)].

There are numerous scientific studies that support the potential benefit of hormone therapy in reducing age-related brain dysfunction (including the risk for Alzheimer's disease) but also others, such as the Women's Health Initiative-Memory Study which failed to reveal beneficial effects of progesterone in reducing neurological senescence (including Alzheimer's). As a result the benefit of hormone therapy is up for debate. One important factor that should be taken into consideration is the type of hormone studied as there are important differences in the neurobiology of natural progesterone and synthetic progestins[(3)].

The term "progesterone" shall be used only to designate the "natural" or "bioidentical" form of this hormone whereas the term "progestin" shall be used in order to designate synthetic progestagens.

Mechanisms underlying progesterone's protective effects

Classical genomic mechanism

This mechanism works via the progesterone receptor (PR) which has been described as a nuclear transcription factor, acting through specific PR elements within the promoter region of target genes to regulate transcription. They are widely spread in both the developing and adult brain. There are two major isoforms of this receptor: PR-B and its N-terminally truncated form PR-A[(1)]. Through these receptors, progesterone activates certain signal transduction pathways, which in turn, trigger cellular events that are relevant and important for neuroprotection such as increasing the expression of brain-derived neutrotrophic factor.

"Non-genomic mechanisms" - Progesterone has been shown to elicit rapid effects on specific signaling pathways including: the cyclic adenosine monophosphate/protein kinase A2, mitogen-activated protein kinases(MAPK)/ extracellular signal-regulated kinases 1 and 2[(3,4)] the phosphatidylinositol-3-kinases/protein-kinase B (Akt) pathway[(5,6)] all of which have been involved in mediating neuroprotective effects. Progesterone induced neuroprotection has not only been correlated with activation of the MAPK and Akt signaling pathways[5] but has also

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been shown to depend on the activation of the MAPK pathway. Activation of these signaling pathways, in turn, may also lead to increased expression of anti-apoptotic proteins such as Bcl-2[7].

Through its metabolites allopregnanolone binds to discrete sites within the hydrophobic domain of the gamma-aminobutyric acid (GABAA) receptor complex, and results in the augmentation of GABA-induced chloride conductance. In addition to the effects of allopregnanolone on the GABAA receptor, as outlined above, it may also elicit protective effects through its actions on the mitochondria[6]. For example, allopregnanolone was reported to inhibit currents associated with the opening of the mitochondrial permeability transition pore (mtPTP)[7], and as such, may help reduce the potential apoptotic consequences of mtPTP opening (such as cytochrome c release) during insult or injury.

Progesterone effects on myelination and remyelination in CNS and PNS

Myelination and remyelination processes require the generation of oligodendrocytes from the oligodendrocyte progenitor cells (OPC)[8,9]. In response to a lesion, OPC proliferate and are recruited to the demyelinated axons where they differentiate into mature oligodendrocytes.

In the PNS, myelin sheaths are formed by Schwann cells, the only glial cell type in peripheral nerves. Peripheral and central myelin also differs in protein content. Whereas PNS and CNS myelin proteins are very different, myelin lipids are qualitatively very similar and only differ quantitatively[10]. The steroid cholesterol is a major lipid constituent of the myelin membrane, comprising about 25% of the total myelin lipids, and this explains why 25% of the total amount of cholesterol present in the human body is localized to the brain[11].

Myelin formation is also under the influence of progesterone, either derived from the steroidogenic endocrine glands or from local synthesis. A role for progesterone in myelin formation was first demonstrated in the PNS, and this original observation was subsequently extended to the CNS.

Early OPC synthesize progesterone and produce its reduced metabolite allopregnanolone, a potent positive allosteric modulator of GABAA receptors. Progesterone indeed indirectly stimulates the proliferation of early OPP through its metabolite allopregnanolone via a bicuculline sensitive mechanism involving GABAA receptors[12]. Importantly, the early OPC express GABAA receptors and also synthesize GABA. These results reveal complex autocrine/paracrine loops in the control of early OPC proliferation, involving interactive neurosteroid and GABA signaling[13].

The effects of progesterone on myelin repair can also be tested in organotypic cultures of cerebellar slices. In organotypic slice cultures of 7-day old rat cerebellum, progesterone was found to also stimulate the proliferation of OPC at later stages of maturation, when they become OPC expressing the chondroitin sulfate proteoglycan and pre-oligodendrocytes co-expressing chondroitin sulfate proteoglycan antigens[14].

When cerebellar slices were exposed to the potent fourth-generation progestin nestorone, designed to selectively target intracellular PR, dense networks of well-organized myelinated fibers were observed. In contrast, another progestin used in contraception and hormone replacement therapy, the 17-OH progesterone derivative medroxyprogesterone acetate (MPA) had no significant effect on the formation of new myelin sheaths. This study also revealed that progestins promote the formation of new myelin sheaths via pleiotropic influences on the proliferation, migration, and differentiation of OPC[15].

Animal studies also demonstrate that progesterone promotes the differentiation of OPC into myelinating oligodendrocytes in adult male rats after spinal cord injury[16]. Further support for progesterone's protective actions in the spinal cord comes from the observation that progesterone has been shown to promote morphological and functional recovery in the Wobbler mouse, an animal model of spinal cord degeneration[17].

The role of progesterone in the myelination of PNS is the local synthesis of myelin observed in sciatic nerve lesion models in rats. Progesterone can induce re-myelination as supported by the increased expression of myelin proteins in the damaged sciatic nerves of both young adult rats and in 22-24-month-old males[18].

In myelinating cultures of Schwann cells and dorsal root ganglion neurons, PR immunostaining was only detected in the neurons, and adding progesterone to the culture medium induced neuron-specific genes. These observations suggested that progesterone may indirectly stimulate Schwann cell myelination by acting on neurons[19].

In peripheral myelin, the transmembrane protein zero (P0) represents the major protein involved in neuron-glial interaction. Mutations in the P0 gene are at the origin of neuropathies (Charcot-Marie-Tooth disease type 1B). In addition to P0 glycoprotein the PNS contains the peripheral myelin protein 22 (PMP22) (involved in myelin assembly and maintenance)(5). The expression of PMP22 was found to be stimulated by the progesterone metabolite allopregnanolone acting via GABA A receptors under the same experimental conditions[20].

Effects of progesterone on cognitive function

Considering an experimental model, the ovariectomised animal is deprived of not just estadiol but of progesterone as well implying that the cognitive deficits recognized may be attributed to loss of circulating progesterone. The effect of progesterone deprivation alone is not well studied and understood.

Studies assessing progesterone effects have been conducted using a model of traumatic brain injury[21], or in experimental models of accelerated neurodegeneration and/or cognitive impairment such as in the triple transgenic mouse model of Alzheimer's disease[22] or the scopolamine-induced memory impairment model[23]. There are, however, a few studies that have described the effects of progesterone on cognitive function in ovariectomised rodents. Frye and colleagues[24] described a beneficial effect of progesterone in an object placement task relative to ovariectomised controls.

In contrast to the beneficial effect of progesterone reported, Chesler and Juraska[25] described that progesterone administration to ovariectomised rats had no effect on spatial learning relative to their age-matched and non-hormone treated ovariectomised controls.

Overall, these studies underscore the complexity by which progesterone may influence cognitive function emphasizes the need for additional studies to better understand the consequences of progesterone on cognitive function, throughout the lifespan.

Progesterone receptor as a therapeutic target for promoting myelination and myelin repair

Despite the widespread use of progestins around the globe, relatively little is known about the effect of long-term treatment in the brain of women during and following their reproductive years. Animal and human studies strongly suggest that progestins have important effects on neurological function, ranging from regeneration in the brain to cognition[25].

The identification of PR as a therapeutic target for promoting myelination and myelin repair suggests new therapeutic benefits for contraceptive progestins, and in particular for fourth- generation 19-nor-progestatives, specifically designed to target the intracellular PR (nestorone, nomegestrol acetate). However, it is important to mention the fact that not all synthetic progestins are the same, and that they belong to different classes with very distinct pharmacological properties and actions. Thus, whereas Nestorone promotes myelin repair and has neuroprotective properties, the progestin MPA is devoid of such beneficial effects and can even become harmful for neural cells[26].

The issue that needs addressing is whether to focus on the therapeutic promises of synthetic progesterone or to use the natural (bioidentical) form. Progestins have higher receptor potency, great selectivity and efficacy but natural progesterone may offer better risk/benefit on the long term (regarding breast cancer and thrombotic risk). Natural progesterone and its derivates (allopregnanolone) have a wider range of effects compared with the synthetic selective progestins that don't have active metabolites. Also progesterone connects to both intracellular and membrane receptors being (PR alfa isoform) in contrast to progestins[27].

Regarding the route of administration it was observed that progesterone has a high rate of destruction in the digestive tract making the administration difficult. Micronized progesterone is a solution having a longer half-life and enhanced bioavailability and efficacy[27]; intravenous administration and intramuscular injections are suited for acute treatments. Also transdermal and vaginal gels have been developed to reach target tissues prior to liver metabolism. The intranasal route of administration could offer the possibility of achieving the desired brain concentration of progesterone required for myelin repair and neuroprotection, opening perspectives both for the efficient acute and long-term use of natural progesterone[28].

Conclusions

The range of neurological and cognitive effects progestins have on the brain make it especially important for researchers to continue to tease apart the circumstances under which progestins may be an advantage or a drawback to the brain, whether during the reproductive years or beyond. ■

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