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Progesterone, BDNF and Neuroprotection

Meharvan Singh and **Chang Su**
Department of Pharmacology and Neuroscience, Institute for Aging and Alzheimer's Disease Research, Center FOR HER, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107 USA

Abstract

While the effects of progesterone in the central nervous system (CNS), like those of estrogen, have generally been considered within the context of reproductive function, growing evidence supports its importance in regulating non-reproductive functions including cognition and affect. In addition, progesterone has well-described protective effects against numerous insults in a variety of cell models, animal models and in humans. While ongoing research in several laboratories continues to shed light on the mechanism(s) by which progesterone and its related progestins exert their effects in the CNS, our understanding is still incomplete. Among the key mediators of progesterone's beneficial effects is the family of growth factors called neurotrophins. Here, we review the mechanisms by which progesterone regulates one important member of the neurotrophin family, Brain-Derived Neurotrophic Factor (BDNF), and provide support for its pivotal role in the protective program elicited by progesterone in the brain.

Progesterone, the natural progestin, is a major gonadal hormone that is synthesized primarily by the ovary in the female, and the testes and adrenal cortex in the male. While progesterone levels are generally higher in the female, it is worth noting that levels of progesterone during the female follicular phase of the menstrual cycle are similar to those seen in males (Strauss and Barbieri, 2004), and thus, may be equally important in males. And while the function of progesterone has historically been considered within the context of reproductive function, it is now clear that progesterone has important effects on multiple organ systems, such as the brain where progesterone can exert protective effects.

Progesterone and Neuroprotection

Progesterone has been reported to exert protective effects in numerous experimental models that mimic a variety of pathogenic aspects of brain dysfunction seen with advanced age or age-related neurodegenerative diseases such as Alzheimer's disease. For example, physiologically relevant concentrations of progesterone have been shown to significantly attenuate oxidative and/or excitotoxic injury resulting from glutamate treatment (Nilsen and Brinton, 2002b, a, 2003, Kaur et al., 2007), glucose deprivation (Goodman et al., 1996), as well as $FeSO_4$- and amyloid β-peptide – induced toxicity (Goodman et al., 1996).

Corresponding Author: Meharvan Singh, Ph.D., Department of Pharmacology and Neuroscience, University of North Texas Health Science Center at Fort Worth, 3500 Camp Bowie Blvd., Fort Worth, TX 76107, Phone: 817-735-5429, FAX: 817-735-0179, meharvan.singh@unthsc.edu.

Progesterone is also an effective neuroprotectant in animal models of stroke. For example, Jiang *et al.* illustrated that the administration of progesterone before middle cerebral artery occlusion (MCAO) resulted in a marked reduction in cerebral infarction and reduced impairments that resulted from the occlusion (Jiang et al., 1996). Interestingly, post-ischemic administration of progesterone was also found to be protective (Kumon et al., 2000, Morali et al., 2005), and resulted in improvements in various functional measures, including the rotarod test, and adhesive-backed somatosensory and neurological scores (Chen et al., 1999). The ability of progesterone to protect even when administered after the insult (albeit within a relatively narrow window) may suggest that both rapid/immediate and long-term mechanisms of progesterone action are involved in the protective effects of progesterone.

Another model in which progesterone has been shown to exert protective effects is in the traumatic brain injury (TBI) model. The administration of progesterone reduces cerebral edema for up to 24 hours after injury. In a rodent model of medial frontal cortex impact injury, progesterone reduced complement factor C3, glial fibrillary acidic protein (GFAP), and nuclear factor kappa beta (NFκB) (Pettus et al., 2005), all of which can be interpreted as protective mechanisms. Progesterone not only facilitates cognitive recovery and reduces secondary neuronal loss caused by edema in ovariectomized female rats after TBI, but also exerts the similar effects in male rats given the same effective dose (Roof et al., 1994). Progesterone also decreased the levels of lipid peroxidation in male rats when administered after TBI (Roof and Hall, 2000).

The protective effects of progesterone are also evident in other regions of the central nervous system in addition to the hippocampus and cerebral cortex. For example, progesterone has also been shown to have a beneficial effect on spinal cord contusion injuries as supported by the work of Thomas *et al.* who found that there was a marked reduction in the size of the lesion and a prevention of secondary neuronal loss with progesterone treatment (Thomas et al., 1999). Additional 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 (Gonzalez Deniselle et al., 2002a, Gonzalez Deniselle et al., 2002b). Progesterone can also induce remyelination 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 (Ibanez et al., 2003). Thus, progesterone may be of potential therapeutic benefit in diseases where demyelination is an important component of its pathogenesis.

While the studies described above were all derived from animal models and cell/tissue culture models, it is worth mentioning that a relatively recently completed phase II, randomized, double-blind, placebo-controlled clinical trial assessing the efficacy of progesterone treatment for acute traumatic brain injury yielded promising results. The data suggested that progesterone treatment can improve functional recovery, at least when administered to those who experienced moderate, but not severe, traumatic brain injury (Wright et al., 2007, Vandromme et al., 2008, Xiao et al., 2008, Junpeng et al., 2011, Wali et al., 2011).

Numerous studies that investigated the effects of progesterone often did so within the context of estrogen treatment. That is to say, a significant proportion of studies compared the effect of estrogen to the effect of the combined administration of estrogen and progesterone. Only more recently, as outlined above, have researchers addressed the influence of progesterone alone. And while there is growing evidence to support the neuroprotective effects of progesterone alone, the influence of progesterone on estrogen's

neuroprotective effects is more equivocal. Some studies suggest that progesterone does not interfere with the effects of estrogens (E2) (Nilsen and Brinton, 2002b, Lorenz et al., 2009, Mannella et al., 2009), while other studies have shown that progesterone or synthetic progestins antagonize the effects of estrogen (Rosario et al., 2006, Carroll et al., 2008, Aguirre and Baudry, 2009, Jayaraman and Pike, 2009, Aguirre et al., 2010, Yao et al., 2011). An example of the capacity of progesterone to antagonize estrogen's effects is described by the work of Murphy and Segal who demonstrated that progesterone antagonizes the effect of E2 on hippocampal spine density (Murphy and Segal, 2000). In addition, McEwen and Woolley showed that in adult as well as in developing brain, progesterone contributed to the loss of hippocampal spines and spine synapses noted across the estrous cycle (McEwen and Woolley, 1994), although progesterone did result initially (within the first 6 hours) in an increase in hippocampal dendritic spine density (Woolley and McEwen, 1993). In contrast, Zhu *et al.* reported a positive influence of progesterone similar to that of E2 on synaptogenesis in the hippocampus of a rat stroke model (Zhao et al., 2011), and Foy *et al.* (Foy et al., 2008) demonstrated that progesterone enhanced LTP and LTD in rat hippocampus. Future studies will undoubtedly clarify the biological basis of this apparent discrepancy, which could be dependent on the experimental model used (reflecting the types of receptors expressed in the model), the concentrations/doses of progesterone applied, the timing of the progesterone relative to that of estrogen, the timing of progesterone relative to the insult, and even potential regional differences in the effects of combined estrogen and progesterone.

BDNF as a neuroprotectant

BDNF belongs to the family of neurotrophins (that include NGF, NT-3 and NT4), which play key roles in the brain to support cell survival and synaptic plasticity (Cohen and Greenberg, 2008, Lu et al., 2008) and is synthesized in both neurons and glia (Causing et al., 1997, Pruginin-Bluger et al., 1997). BDNF is synthesized as a glycosylated precursor (pre-pro-BDNF), processed into a 35 kDa pro-BDNF, and then can be converted into the 14 kDa mature BDNF intracellularly or extracellularly (Matsumoto et al., 2008, Lu et al., 2005). BDNF released from cells exerts its functions via binding to TrkB (a tyrosine kinase trk family of receptors) or $p75^{NTR}$ receptor (Pruginin-Bluger et al., 1997, Matsumoto et al., 2008, Minichiello, 2009, Yoshii and Constantine-Paton, 2010). Delineating the effects of pro-versus mature BDNF is critical, because they often exert opposite biological functions: while mature BDNF binds to the TrkB receptor to influence neuronal survival, differentiation, and promote LTP, pro-BDNF binds preferentially to $p75^{NTR}$ and can induce neuronal apoptosis and promote LTD (see (Lu et al., 2005) and references cited therein). Moreover, it has been proposed that neuronal dysfunction or atrophy consequent to aging or age-associated diseases may result from not only decreases in mature neurotrophin expression or function (Phillips et al., 1991, Connor et al., 1997, Hock et al., 1998), but potentially, to *increased* accumulation of the pro-neurotrophins. In fact, Fahnestock and colleagues have described that the pro-neurotrophin for NGF (pro-NGF) is increased in AD brains (Fahnestock et al., 2001).

As suggested above, there is strong evidence to support the role of BDNF in synaptic plasticity and cognitive function (Murer et al., 2001), and as such, alteration in its function and/or expression has been implicated in the pathophysiology of aged-related neurodegenerative diseases including AD and PD (Ferrer et al., 1999, Tapia-Arancibia et al., 2008, Zuccato and Cattaneo, 2009), and conversely, restoring BDNF expression and/or function may be therapeutic. A large body of research indicates a role of BDNF as a protectant in stroke. Interventions that improve recovery of function are often associated with increased BDNF levels in the penumbra. For example, Lazarovici et al., recently reported that pituitary adenylate cyclase activating peptide (PACAP) exhibits its protective

effects in rat stroke models by inducing BDNF expression and release as well as activating TrkB receptor (Lazarovici et al., 2012). Ishrat et al. also showed that BDNF mediated progesterone's effect to reduce ischemic lesion size and edema in rats underwent permanent focal cerebral ischemia (Ishrat et al., 2012). Furthermore, direct injection of recombinant adeno-associated virus (rAAV) carrying BDNF gene into a rat focal ischemic lesion decreased cell death (Zhang et al., 2011). Conversely, attenuating BDNF levels or its effects following cerebral ischemia often reduces recovery of function (Chen et al., 2005, Ploughman et al., 2009). It is worthwhile to mention that non-neuronal cells (such as astrocytes, microglia and endothelial cells) also produce substantial amount of BDNF after ischemic stroke (Bejot et al., 2011), therefore, these cells may contribute significantly to the BDNF-dependent recovery. BDNF has also been implicated as a neuroprotectant in TBI (for review, see (Kaplan et al., 2010) and references cited therein). Conditional knockout of BDNF in the hippocampus increased death of adult-born immature neurons following TBI (Gao and Chen, 2009). Conversely, induction of BDNF and its associated proteins is associated with therapeutic improvement and recovery of function after TBI (Griesbach et al., 2004, Wu et al., 2008).

Mechanistically, the protection afforded by BDNF may be elicited through multiple mechanisms including the activation of specific signaling pathways, such as the MAPK and PI-3K pathways. For example, exogenous BDNF protects primary cortical neurons from apoptosis in a dose-dependent manner (Hetman 1999). While BDNF increases the phosphorylation of PI3K and Akt (as an indicator of their activation), pharmacological inhibition of the PI-3K pathway by LY294002 prevents the neuroprotective effects of BDNF in primary cortical neurons (Hetman et al., 1999). Similarly, BDNF induces a significant increase of ERK1/2 phosphorylation/activation, and pharmacological inhibition of the ERK1/2 pathway by PD98059 greatly reduced BDNF's neuroprotective effects. In addition, intracerebroventricular administration of BDNF to postnatal day 7 rats resulted in phosphorylation of ERK1/2 and Akt within minutes (Han and Holtzman, 2000), and pharmacological inhibition of ERK inhibited the ability of BDNF to block hypoxia/ischemia-induced caspase-3 activation and tissue loss (Han and Holtzman, 2000). Given that progesterone can not only elicit the rapid activation of both the ERK/MAPK and Akt signaling pathways in the central nervous system (Singh, 2001, Nilsen and Brinton, 2002b, 2003), but induce the expression of BDNF as well, either direct activation of these signaling pathways (i.e., direct coupling with activated progesterone receptors) or the regulation of the synthesis and release of BDNF may underlie progesterone's protective effects.

BDNF as a mediator of progesterone's protective effects

Our laboratory (Singh et al., 1995, Kaur et al., 2007) and that of others (Gonzalez et al., 2004, Gonzalez Deniselle et al., 2007) have shown that progesterone increases the expression of BDNF in various experimental systems, including explants of the cerebral cortex, the injured spinal cord and in degenerating Wobbler motorneurons. For example, treatment of cortical explants with a physiologically relevant concentration of progesterone (100 nM) for 24 hours induces an approximately 75% increase in both BDNF mRNA and protein expression (Kaur 2007), an effect that appeared to be relevant to the protective effects of progesterone (Kaur et al., 2007). Further, the "classical" intracellular/nuclear PR was determined to be the principle mediator of the effect of progesterone on BDNF expression since this effect was inhibited by the pharmacological inhibitor of the PR, RU486, and was lost in PR knockout mice (Jodhka et al., 2009).

While synthesis is important, the capacity to promote the release of BDNF is also important, since as described above, regulation of cell signaling pathways consequent to BDNF action (i.e., through interaction with the TrkB receptor) may be an equally important way by which

progesterone elicits its effects. We recently reported that progesterone triggers a significant release of BDNF from glia (Su et al., 2012). Interestingly, the classical PR was not involved in this process, as our cultured astrocytes lacked the expression of PR; instead, progesterone's effect on BDNF release is mediated through a novel membrane-associated progesterone receptor, Pgrmc1, and its associated activation of the ERK5 signaling cascade (Su et al., 2012). Since the classical PR mediates the effect of progesterone on BDNF expression, and Pgrmc1 appears to mediate the effect of BDNF on release, our laboratory proposes that both these receptor mechanisms are required to afford sustainable protective effects where progesterone, through the PR, replenishes BDNF stores while simultaneously promoting the release, and thus, availability of BDNF to surrounding cells (an effect mediated by Pgrmc1).

The capacity of progesterone to regulate BDNF may also be relevant to the cognitive enhancing role of progesterone. Indeed, there are several studies that support the role of BDNF in regulating synaptic plasticity in the brain, including LTP (Schuman, 1999). In particular, BDNF appears to be required for "late" LTP, a component of LTP that requires *de novo* synthesis of mRNA and protein (Bliss and Collingridge, 1993, Nguyen and Kandel, 1996). Among the mechanisms that are thought to play a role in mediating the effects of BDNF on LTP include the phosphorylation of NMDA receptors, which in turn, alter the function of the receptor. Indeed, both the NR1 (Suen et al., 1997) and the NR2B (Lin et al., 1998) subunits of the NMDA receptor have been described as targets of BDNF-induced signaling. Furthermore, the BDNF-induced phosphorylation of these subunits is associated with functional changes in the receptor, such as increasing the open probability of the NMDA receptor channel (Crozier et al., 1999, Levine and Kolb, 2000). Several of the signaling pathways elicited by progesterone have also been implicated in regulating LTP, as pharmacological or genetic inhibition/disruption of these pathways can inhibit LTP relevant NMDA receptor phosphorylation (Xu et al., 2006), BDNF-induced increase in fEPSPs (Ying et al., 2002) and produce frank deficits in hippocampal LTP (Chen et al., 2006). As such, progesterone may regulate LTP (and thus, influence cognitive function) by direct activation of relevant cell signaling pathways (i.e., through direct coupling to progesterone receptors), or alternatively, influence LTP through its effects on BDNF release, which in turn, activates the signaling pathways that phosphorylate NMDA receptors.

As discussed above, the protective effects of synthesized neurotrophins may depend on the ratio of relative abundance of the pro- and mature forms of the neurotrophin since pro-neurotrophins, which bind preferentially to the p75 "pan" neurotrophin receptor may promote cell death, while mature neurotrophins that preferentially bind to their cognate Trk receptor, elicit signaling events consistent with cell survival. Recently, the laboratory of Dr. Donald Stein reported that progesterone can differentially regulate the expression of pro- versus mature neurotrophins. Specifically, in a model of traumatic brain injury (TBI), progesterone elicited a decrease in the pro-apoptotic pro-NGF while increasing the level of mature NGF. While this effect on NGF (pro- and mature) appears consistent with the protective effects of progesterone, the observed effects of progesterone on pro-versus mature BDNF were not. In fact, progesterone not only decreased the expression of pro-BDNF, but reduced the expression of mature BDNF and its cognate receptor, TrkB (Cekic et al., 2012). Undoubtedly, future studies will help clarify this apparent discrepancy.

Metabolites of progesterone and their influence on BDNF

In terms of the receptor pharmacology associated with progesterone's effects on the brain, there now exist numerous candidates, in addition the "classical" progesterone receptor, which is generally described as a nuclear transcription factor, acting to regulate transcription of such genes as BDNF. More recently, however, membrane receptors for progesterone have

also been proposed. And though their existence has been suggested for many years, based primarily on the existence of specific, displaceable binding sites observed in synaptosomal membrane preparations (Towle and Sze, 1983, Ke and Ramirez, 1990), only recently have membrane-associated progesterone receptors been cloned. For example, Zhu and colleagues discovered a novel membrane-associated progesterone receptor, termed mPR (Zhu et al., 2003a), that has a predicted seven transmembrane-spanning domain, and is coupled to the $G_{i/o}$ class of G-proteins (Zhu et al., 2003b). Other membrane progesterone receptors include Pgrmc1, an apparently neuron-specific membrane progesterone receptor (Meyer et al., 1996, Falkenstein et al., 1998, Krebs et al., 2000), that is involved in numerous aspects of cell function, ranging from neuronal development (Sakamoto et al., 2004), steroidogenesis (Min et al., 2004), regulation of reproductive behavior (Krebs et al., 2000), and as described above, potentially in the neuroprotective effects of progesterone.

However, in considering the neuroprotective effects of progesterone, one must also consider the possibility that the effects of progesterone may be mediated by its metabolite, allopregnanolone (3α, 5α tetrahydroprogesterone or THP). Allopregnanolone is a positive allosteric modulator of the GABA-A receptor (see (Deutsch et al., 1992) for review), and as such, its neuroprotective effects may be related to its ability to attenuate excitotoxicity associated with brain injury or insult. In fact, several studies have shown that allopregnanolone treatment reduces several deficits or consequences of traumatic brain injury. For example, allopregnanolone decreased inflammatory cytokine levels (He et al., 2004a) and decreased cell death and cognitive deficits (Djebaili et al., 2004, He et al., 2004a) consequent to traumatic brain injury. Indeed, allopregnanolone has been suggested to play a role in mediating the protective effects of progesterone (Ciriza et al., 2004) (Djebaili et al., 2004, He et al., 2004a, He et al., 2004b, Vitarbo et al., 2004, Ardeshiri et al., 2006, Sayeed et al., 2009). Moreover, allopregnanolone has also been shown to exert significant effects on neurogenesis (see (Wang et al., 2008) and references cited therein for review). Interestingly, it has been shown that allopregnanolone may also elicit its protective effects through the regulation of BDNF (see (Nin et al., 2011) and references cited therein), although the precise mechanism by which allopregnanolone elicits BDNF (i.e., what receptor(s) allopregnanolone works through) is still unclear.

Is there a correlation between clinically used progestins and their influence on BDNF?

Medroxyprogesterone Acetate (MPA) is a synthetic progestin often used in conjunction with estrogens to reduce the risk of certain cancers (uterine cancer, for example) resulting from unopposed estrogen therapy (Gambrell, 1986, Hirvonen, 1996). However, we and others have found that not all progestins are created equal when considering their cytoprotective effects. For example, progesterone, but not MPA, was protective against glutamate toxicity in both cerebral cortical explants (Kaur et al., 2007) and in primary dissociated hippocampal neurons (Nilsen and Brinton, 2002b). This disparity between the effects of P4 and MPA has also been observed *in vivo*. For example, a study using rhesus monkeys illustrated that the combined administration of estrogen and progesterone protects against coronary vasospasm, whereas the co-administration of MPA with estrogen obviated this effect (Miyagawa et al., 1997). This disparity between progesterone and MPA is also evident in humans, where progesterone administration to post-menopausal women enhanced the protective effects of estrogen on exercise-induced myocardial ischemia whereas MPA did not (Rosano et al., 2000).

While the discrepancy between the protective effects of progesterone and MPA may be attributed to differential regulation of ERK translocation (Nilsen and Brinton, 2003), anti-apoptotic protein regulation (Nilsen and Brinton, 2002b), and calcium homeostasis (Nilsen

and Brinton, 2002b), it appears that a fundamental difference in the regulation of BDNF may also underlie the difference between progesterone and MPA. For example, our laboratory has shown that that while progesterone increases the expression (both mRNA and protein) of BDNF in cerebral cortical cultures, MPA suppresses BDNF levels (Jodhka et al., 2009).

Summary

The information presented here supports the conclusion that progesterone is protective and that the regulation of BDNF may be a key mediator of such protection. Progesterone regulates not just the intracellular content of BDNF (mRNA and protein), an effect mediated by the classical progesterone receptor, but is also capable of promoting the release of BDNF through activation of a putative membrane progesterone receptor. This release of BDNF would, in turn, lead to the activation of TrkB receptors located on the cell surface of adjacent cells and activate a variety of pro-survival cell signaling pathways that include the ERK/MAPK and PI3K/Akt signaling pathways. Interestingly, the capacity of a progestin to exert neuroprotective effects appears to correlate with its capacity to increase BDNF levels. Such a relationship not only supports the key role of BDNF in these protective effects but also underscores the fact that not all progestins are created equal, particularly within the context of their influence on brain function. Such insight may guide the development of more effective therapeutic formulations for treatment of the menopause and various (neurodegenerative) diseases whose incidence increases during the post-menopausal period.

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Highlights

- Progesterone is neuroprotective
- Progesterone increases the expression of BDNF
- Progesterone's protective effects are mediated, in part, by enhancing the expression and/or function of BDNF