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Review

Progesterone and neuroprotection

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ABSTRACT

This article is part of a Special Issue "Hormones & Neurotrauma".

Numerous studies aimed at identifying the role of estrogen on the brain have used the ovariectomized rodent as the experimental model. And while estrogen intervention in these animals has, at least partially, restored cholinergic, neurotrophin and cognitive deficits seen in the ovariectomized animal, it is worth considering that the removal of the ovaries results in the loss of not only circulating estrogen but of circulating progesterone as well. As such, the various deficits associated with ovariectomy may be attributed to the loss of progesterone as well. Similarly, one must also consider the fact that the human menopause results in the precipitous decline of not just circulating estrogens, but in circulating progesterone as well and as such, the increased risk for diseases such as Alzheimer's disease during the postmenopausal period could also be contributed by this loss of progesterone. In fact, progesterone has been shown to exert neuroprotective effects, both in cell models, animal models and in humans. Here, we review the evidence that supports the neuroprotective effects of progesterone and discuss the various mechanisms that are thought to mediate these protective effects. We also discuss the receptor pharmacology of progesterone's neuroprotective effects and present a conceptual model of progesterone action that supports the complementary effects of membrane-associated and classical intracellular progesterone receptors. In addition, we discuss fundamental differences in the neurobiology of progesterone and the clinically used, synthetic progestin, medroxyprogesterone acetate that may offer an explanation for the negative findings of the combined estrogen/progestin arm of the Women's Health Initiative-Memory Study (WHIMS) and suggest that the type of progestin used may dictate the outcome of either pre-clinical or clinical studies that addresses brain function.

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The biology of progesterone

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. The "classical" mechanism by which progesterone elicits its effects is via the progesterone receptor (PR), which like the estrogen receptor (ER), has classically been described as a nuclear transcription factor, acting through specific progesterone response elements (PRE) within the promoter region of target genes to regulate transcription. These progesterone receptors are widely distributed in the developing and adult brain (for reviews, see Kato et al.,

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1994; MacLusky and McEwen, 1980), and as such, supports various brain regions as normal targets of progesterone. Two major isoforms of the classical progesterone receptor exist, PR-B, and its N-terminally truncated form, PR-A [for a review, see (Conneely and Lydon, 2000). The latter has been shown to exert negative control of not only PR-B-mediated transcription, but that mediated by the ER and glucocorticoid receptor as well (Vegeto et al., 1993). This negative regulation of ER function by a PR may underlie, at least in part, the mechanism by which progestins functionally antagonize the effects of estrogen. For example, progesterone can inhibit estrogen's ability to increase serum levels of 1,25-dihydroxyvitamin D (Bikle et al., 1992), whose consequence may be to antagonize estrogen's beneficial effects on the bone. Relevant to hormone therapy, the functional antagonism exerted by progestins on estrogen's actions also underlie the rationale for combined estrogen and progestin therapy in women with an intact uterus, as the addition of a progestin reduces the risk of uterine cancer associated with unopposed estrogen therapy (Hirvonen, 1996). However, the relationship between progesterone and estrogen receptors may not always be antagonistic. For example, Migliaccio et al. (1998), demonstrated not only a physical interaction of the progesterone receptor with the estrogen receptor, but that this association was necessary for progesterone to elicit the activation of a signal transduction pathway, the mitogen activated protein kinase (MAPK) pathway, in mammary tumor cells.

In addition to the regulation of gene transcription, progesterone can also elicit its effects via non-genomic mechanisms such as through the activation of signal transduction pathways. Among those second messenger/signal transduction systems now known to be activated by progesterone include cAMP/PKA (Collado et al., 1985), MAPK (ERK1/2) (Migliaccio et al., 1998; Singh, 2001) and the PI-3K/Akt pathway (Singh, 2001). Activation of such signaling pathways has, in fact, been implicated in its neuroprotective effects (see below).

Progesterone-induced neuroprotection

Progesterone has been reported to exert protective effects in a variety of experimental models that mimic certain 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 injury resulting from glutamate (Kaur et al., 2007; Nilsen and Brinton, 2002a,2002b, 2003) and glucose deprivation-induced toxicity (Goodman et al., 1996), and also protects against $FeSO_4$- and amyloid β-peptide-induced toxicity in primary hippocampal cultures (Goodman et al., 1996).

Progesterone is also an effective neuroprotectant in animal models of stroke. For example, Jiang et al. (1996) 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. 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. Progesterone has also been shown to reduce the amount of cell death following an acute episode of global ischemia (Cervantes et al., 2002), and is thought to be related to the ability of progesterone to reduce lipid peroxidation, the generation of isoprostanes (Roof et al., 1997) and the expression of pro-inflammatory genes (Pettus et al., 2005). It is worth pointing out that in these studies, the dose of progesterone used may also be relevant since supraphysiological serum/plasma levels of progesterone were achieved. With such doses, the resulting levels of allopregnanolone, the major progesterone metabolite, could underlie some of the neuroprotective levels (see below for discussion of allopregnanolone and neuroprotection).

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 h 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 also decreased the levels of lipid peroxidation in male rats when administered after TBI (Roof and Hall, 2000).

Interestingly, there appears to be a sex difference in terms of the severity of impairment following TBI. Females appeared to have less spatial learning impairments when compared to their male counterparts. And though the lesion size was similar, females exhibited less ventricular dilation indicating lower edema and water retention (Attella et al., 1987). In fact, direct assessments of edema reveal that progesterone treatment significantly attenuates the level of edema seen in injured animals in contrast to non-progesterone treated animals that had undergone experimental TBI (Roof et al., 1996).

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. (1999) who found that there was a marked reduction in the size of the lesion and a prevention of secondary neuronal loss with progesterone treatment. 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 (Gonzalez Deniselle et al., 2002a,2002b). Progesterone can also 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 (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 (Junpeng et al., 2011; Vandromme et al., 2008; Wali et al., 2011; Wright et al., 2007; Xiao et al., 2008).

While several studies have suggested that progesterone does not interfere with the beneficial effects of estrogens (E2) (Lorenz et al., 2009; Mannella et al., 2009; Nilsen and Brinton, 2002b), other studies have shown that progesterone or synthetic progestin antagonizes the protective effects of estrogen (Aguirre and Baudry, 2009; Aguirre et al., 2010; Carroll et al., 2008; Jayaraman and Pike, 2009; Rosario et al., 2006; Yao et al., 2011). For example, Murphy and Segal (2000) demonstrated that progesterone antagonizes the effect of E2 on hippocampal spine density. 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 h) 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. (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 include the experimental model being used (reflecting the types of receptors expressed in the model), the concentrations/doses of progesterone used, 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.

Mechanisms underlying progesterone's protective effects

Numerous mechanisms of action likely underlie the protective effects of progesterone. The classical genomic mechanism of progesterone action, for example, may be involved in the regulation of neurotrophin expression (Kaur et al., 2007), which in turn, could promote cell survival. Alternatively, progesterone may act through novel receptor systems, such as the membrane PR or the sigma receptor (another putative receptor for progesterone), to activate certain signal transduction pathways, which in turn, triggers cellular events that are relevant and important for neuroprotection. Additionally, major metabolites of progesterone, such as allopregnanolone, have been reported to participate in the neuroprotective effects of progesterone (Ciriza et al., 2004).

With regards to the relationship between progesterone and neurotrophins, we (Kaur et al., 2007; Singh et al., 1995) and others (Gonzalez Deniselle et al., 2007; Gonzalez et al., 2004; Sohrabji et al., 1995) have shown that steroid hormones, including progesterone, increase the expression of BDNF. Further, we found that neurotrophin signaling was necessary for progesterone induced protection (Jodhka et al., 2009).

With respect to "non-genomic" or cell signaling mechanisms underlying progesterone's protective effects, progesterone has been shown to elicit rapid effects on specific signaling pathways including the cAMP/PKA (Collado et al., 1985), MAPK (ERK1/2) (Migliaccio et al., 1998; Nilsen and Brinton, 2002b; Singh, 2001) and the PI-3K/Akt pathway (Singh, 2001), all of which have been implicated in mediating neuroprotective effects. Progesterone-induced neuroprotection has not only been correlated with activation of the MAPK and Akt signaling pathways (Nilsen and Brinton, 2002b, 2003) but has also been shown to depend on the activation of the MAPK pathway (Kaur et al., 2007). Activation of these signaling pathways, in turn, may also lead to increased expression of anti-apoptotic proteins such as Bcl-2 (Nilsen and Brinton, 2002b).

Another mechanism by which progesterone can exert protective effects is through its metabolites, which in turn, can interact with membrane-associated receptors coupled to ion-channels, such as the $GABA_A$ receptor system (for a review, see Deutsch et al., 1992). Such metabolites include allopregnanolone (or 3α, 5α tetrahydroprogesterone), which bind to discrete sites within the hydrophobic domain of the $GABA_A$ receptor complex, and result in the potentiation of GABA-induced chloride conductance. Indeed, allopregnanolone has been suggested to play a role in mediating the protective effects of progesterone (Ardeshiri et al., 2006; Djebaili et al., 2004; He et al., 2004a,2004b; Sayeed et al., 2009; Vitarbo et al., 2004). In addition to the effects of allopregnanolone on the $GABA_A$ receptor, as outlined above, allopregnanolone may also elicit its protective effects through its actions on the mitochondria (Robertson et al., 2006). For example, allopregnanolone was reported to inhibit currents associated with the opening of the mitochondrial permeability transition pore (mtPTP) (Sayeed et al., 2009), and as such, may help reduce the potential apoptotic consequences of mtPTP opening (such as cytochrome c release) during insult or injury.

In addition to the allosteric effects described above, progesterone itself may have non-allosteric influences on the $GABA_A$ receptor. Progesterone may influence the $GABA_A$ receptor via the activation of a signal transduction pathway, which in turn, influences GABA-gated currents through phosphorylation of discrete sites within certain subunits of the $GABA_A$ receptor (Bell-Horner et al., 2006; Vasan et al., 2003). Since the regulation of the $GABA_A$ receptor has been shown to modulate cell survival, particularly in models of excitotoxicity, the regulation of the $GABA_A$ receptor by progesterone may be relevant to the protective effect of progesterone seen against kainate-induced seizure activity and subsequent cell death (Hoffman et al., 2003).

Progesterone and cognitive function

When considering the ovariectomized animal, it is important to recognize that this surgical intervention results in the loss of not just estradiol, but of progesterone as well. As such, the cognitive deficits we and others have observed following ovariectomy may have been contributed by the loss of circulating progesterone as well. And though numerous studies, including those from our laboratory, have clearly described the neuroprotective effects of progesterone against a wide array of insults and injuries (see above), the effect of progesterone alone on cognitive function is considerably less well studied and understood. Moreover, interpretation of the data from the WHI that described an accelerated decline in cognitive function in the estrogen plus progestin treated group is complicated by the fact that the effects of progestins on learning and memory is poorly understood.

Those studies that have assessed progesterone's effects on cognitive function have generally done so within the context of an injury, such as traumatic brain injury (Roof et al., 1997), or in experimental models of accelerated neurodegeneration and/or cognitive impairment such as in the triple transgenic mouse model of Alzheimer's disease (3xTg-AD) (Carroll et al., 2007), or the scopolamine-induced memory impairment model (Tanabe et al., 2004). In these models, progesterone helps to preserve cognitive performance. There are, however, a few studies that have described the effects of progesterone on cognitive function in ovariectomized rodents. Frye et al. (2007) described a beneficial effect of progesterone in an object placement task relative to ovariectomized controls. Interestingly, as seen with estradiol, the effectiveness of progesterone required that progesterone be administered within a specific window following "training", suggesting that the effectiveness of progesterone may be dependent on time (or age). Mechanistically, progesterone may either directly, or indirectly through the regulation of BDNF (see above) activate signaling pathways, such as the ERK/MAPK and PI-3K/Akt pathways which, in turn, can regulate LTP (long-term potentiation), the synaptic substrate for learning and memory (Chen et al., 2006; Xu et al., 2006; Ying et al., 2002).

In contrast to the beneficial effect of progesterone reported, Chesler and Juraska (2000) described that progesterone administration to ovariectomized rats had no effect on spatial learning relative to their age-matched and non-hormone treated ovariectomized controls. Quite interestingly, studies from one laboratory have described that ovariectomy of aged rats does not impair spatial memory, but rather enhances it (Bimonte-Nelson et al., 2003, 2004). And further, progesterone counteracted the beneficial effects of ovariectomy. It is worth pointing out, however, that the aged Fisher-344 rats in these studies were likely pseudopregnant, having elevated progesterone levels (and low estradiol levels). In fact, the elevated levels of progesterone during pseudopregnant estropause have been implicated in the impaired spatial cognitive performance of these rats (Warren and Juraska, 2000). Overall, these studies underscore the complexity by which progesterone may influence cognitive function as a function of age, and at the very least, suggest that additional studies are required to better understand the consequences of progesterone on cognitive function, throughout the lifespan.

Receptor pharmacology of progesterone's protective effects

It is clear that the classical, intracellular/nuclear PR certainly plays an important role in mediating the effects of progesterone. For example, our laboratory has determined that the ability of progesterone to increase the expression (mRNA and protein levels) of brain-derived neurotrophic factor (BDNF), a key mediator of progesterone's protective effects, requires the classical PR (Jodhka et al., 2009). Further, Cai

et al. (2008) have implicated the classical/intracellular PR in the protective effects of progesterone against an experimental model (middle cerebral artery occlusion) of stroke. More recently, Liu et al. (2012), described the key role of the classical PR in neuroprotection after experimental stroke, using the PR knockout model. This experimental model (at least the homozygous knockout) has clear reproductive behavior deficits (Conneely and Lydon, 2000), but does not appear to, in and of itself, result in overt phenotypic changes in brain morphology.

However, evidence also exists for alternative mechanisms of action, including that which involves integral membrane progesterone receptors. For example, the effect of progesterone has been reported in the brain of PR knock-out (PRKO) mice (Krebs et al., 2000), suggesting PRs other than the classical PR may mediate the effect of progesterone in the CNS. In fact, several lines of evidence recently obtained suggest that the rapid effects of progesterone are mediated by cell membrane-associated PRs expressed in the brain (Balasubramanian et al., 2008a,2008b; Liu et al., 2009; Tokmakov and Fukami, 2009). If nothing else, progesterone's high degree of lipophilicity (having a logP value, or octanol/water partition coefficient, of approximately 4), may be consistent with the idea that progesterone interacts with a plasma membrane associated receptor.

Membrane receptors for progesterone, though proposed for many years based on the existence of specific, displaceable binding sites observed in synaptosomal membrane preparations (Ke and Ramirez, 1990; Towle and Sze, 1983), have only recently been cloned. For example, Zhu and colleagues discovered a novel membrane-associated progesterone receptor, termed mPR (Zhu et al., 2003a), that has a predicted a 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 25-Dx (also called Pgrmc1), an apparently neuron-specific membrane progesterone receptor (Falkenstein et al., 1998; Krebs et al., 2000; Meyer et al., 1996), that is involved in numerous aspects of cell function, ranging from neuronal development (Sakamoto et al., 2004), steroidogenesis (Min et al., 2004), regulation of CSF production and osmoregulation (Meffre et al., 2005), and the regulation of reproductive behavior (Krebs et al., 2000). Though our laboratory has determined that the classical PR, mPRα, mPRβ and Pgrmc1 are expressed in our experimental models of the CNS wherein we have shown progesterone-induced neuroprotection, we have recently determined that while progesterone's ability to increase BDNF expression is dependent on the classical PR (Jodhka et al., 2009), it is the membrane associated receptor, Pgrmc1, that mediates the effect of progesterone on BDNF release. Further, this effect on BDNF release appears to be mediated by ERK5 (Su and Singh, unpublished observations). Collectively, we believe that these effects on BDNF are critical to progesterone's neuroprotective capacity (Kaur et al., 2007). Moreover, a putative ligand of membrane associated progesterone receptors, the BSA-conjugated progesterone (P4-BSA), that does not bind to the intracellular localized classical PR, fails to increase BDNF levels but yet, is effective in increasing the phosphorylation of ERK1/2 (Jodhka et al., 2009), another proposed mediator of progesterone's neuroprotective effects (Kaur et al., 2007). As such, the ability of a progestin to have maximal neuroprotective efficacy may depend on the complement of progesterone receptors that it is capable of binding/activating.

And finally, progesterone has also been found to interact with sigma 1 (σ_1) receptor (Selmin et al., 1996; Seth et al., 1998). Given the reported role of the sigma 1 receptor in neuroprotection (for a review, see Maurice et al., 2006), this mechanism may also be relevant to progesterone's protective actions.

Why the type of progestin matters

It is estimated that by 2010, the population of women between the ages of 45 and 64 will reach approximately 42 million (U.S. Census Bureau. Projected population of the United States, by Age and Sex: 200 to 2050. www.census.gov/ipc/www/usinterimproj/ Internet release date: March 18, 2004). Among the health-related changes and decisions these women will need to consider include whether or not to consider the use of hormone therapy for not just the management of menopausal symptoms, but potentially, to help maintain a healthy brain. And though numerous basic science, epidemiological and some clinical studies have supported the potential benefit of hormone therapy in reducing the incidence of age-associated brain dysfunction (including reducing the risk for Alzheimer's disease), recent results from the Women's Health Initiative-Memory Study (WHIMS) failed to reveal beneficial effects in reducing the risk of Alzheimer's disease or "all-cause" dementia. As a consequence, these reports left the field unsettled as to the future of hormone therapy. Since the publication of these studies, it became apparent that there were important caveats to the data that needed to be considered. Among these included consideration of the type of hormone used. Indeed there are important differences in the neurobiology of two major progestins, the "natural" progestin, progesterone, and the synthetic medroxyprogesterone acetate (MPA), the most commonly used progestin in hormone therapy regimens.

Medroxyprogesterone acetate (MPA), a synthetic progestin derived from 17α-hydroxyprogesterone, is often used in conjunction with estrogens to reduce the risk of certain cancers (cervical cancer, for example) resulting from unopposed estrogen therapy (Gambrell, 1986; Hirvonen, 1996). First, though both progesterone and MPA can bind to the classical PR, it is important to recognize that there are important pharmacological and pharmacokinetic differences between MPA and progesterone. For example, orally administered MPA does not undergo any first pass effects (Schindler et al., 2003), unlike progesterone. Furthermore, MPA has little binding affinity for sex hormone binding globulin (Schindler et al., 2003). In addition to differences in bioavailability and half-life, MPA also displays many non-progestagenic effects (Schindler et al., 2003), including the ability to bind to the androgen receptor (AR) where it acts as a partial agonist (Winneker et al., 2003) with a binding affinity (Kd) of approximately 2.1 nM (Hackenberg et al., 1990). Progesterone, in contrast, does not bind to the AR (Schindler et al., 2003). MPA can also bind to, and activate, glucocorticoid receptors (Koubovec et al., 2005; Schindler et al., 2003) with an effective concentration (EC50) that is nearly 300-fold lower than that for progesterone (Koubovec et al., 2005).

While progesterone and MPA may be equally effective at reducing the uterotrophic effects of unopposed estrogen treatment, their effects on the brain are far from identical. In fact, it has become increasingly clear that while progesterone is neuroprotective, MPA is not. For example, our laboratory described that in cerebral cortical explants, the difference in neuroprotective efficacy between progesterone and MPA may have been attributed to their differential regulation of BDNF. Specifically, while progesterone increased both the mRNA and protein levels of BDNF in the cerebral cortex, MPA treatment resulted in a substantial inhibition (Jodhka et al., 2009). Combined with the observation that progesterone's protective effects may be dependent on neurotrophin signaling (Kaur et al., 2007), this inhibition of BDNF expression by MPA may not just be without effect, but may actually have adverse consequences to brain function. Similarly, the Brinton laboratory has shown in hippocampal cultures that while progesterone is protective, MPA is not. In this model, the protective effects of progesterone appeared to be mediated, in part, by attenuating the glutamate-induced increase in intracellular Ca^{2+} levels. MPA, in contrast, failed to alter the glutamate-induced influx of Ca^{2+}. Of significance was that MPA not only failed to elicit protective effects, but also blocked the beneficial effect of estradiol. In sharp contrast, progesterone did not inhibit the effect of estradiol (Nilsen and Brinton, 2002a). Furthermore, while some of the neuroprotective effects of progesterone are mediated by its neuroactive metabolite, alloprognanolone (see discussion above), it is unclear if MPA is a substrate for the progesterone metabolizing enzymes 5alpha-reductase and 3alpha-hydroxysteroid dehydrogenase. Instead, MPA has

Table 1
Comparison of the neuroprotection-relevant effects of progesterone and medroxyprogesterone acetate (MPA).

Characteristic/endpoint	Progesterone (P4)	MPA	Supporting reference(s)
Binding to PR	Yes	Yes	Numerous references citing binding of P4 to PR.
Binding to AR	No	Yes	Hackenberg et al. (1990); Winneker et al. (2003); Schindler et al. (2003).
Binding to GR	No	Yes	Schindler et al. (2003); Koubovec et al. (2005)
Neuroprotective	Yes	No	Roof et al. (1996, 1997); Nilsen and Brinton (2002a), Nilsen and Brinton (2003); Jodhka et al. (2009); and others (cited within this manuscript).
ERK1/2 phosphorylation	Yes	Yes	Singh (2001); Nilsen and Brinton (2002a, 2003); Kaur et al. (2007)
Nuclear translocation of ERK1/2	Yes	No	Nilsen and Brinton (2003)
Conversion to allopregnanolone	Yes	No	Numerous references support conversion of P4 to allopregnanolone
Regulation of BDNF	Increase	No effect/decrease	Kaur et al. (2007); Jodhka et al. (2009)

Abbreviations: MPA: medroxyprogesterone acetate; PR: progesterone receptor; AR: androgen receptor; GR: glucocorticoid receptor; ERK: extracellular-signal regulated kinase; P4: progesterone; BDNF: brain-derived neurotrophic factor.

been shown to inhibit the biosynthetic enzymes associated with the conversion of progesterone to allopregnanolone. Thus, both the inability of MPA to be converted to neuroactive steroid metabolites in conjunction with its effect in reducing potential conversion of progesterone to allopregnanolone may contribute to its lack of neuroprotection.

As stated above, progesterone's protective effects, in at least two neuronal models (cerebral cortical neurons and hippocampal neurons), was dependent on activation of the ERK/MAPK pathway (Kaur et al., 2007; Nilsen and Brinton, 2002a, 2003). While both progesterone and MPA can elicit ERK phosphorylation, only progesterone treatment resulted in nuclear translocation of ERK (Nilsen and Brinton, 2003), the consequence of which is likely to regulate key genes, whose protein products may enable more long term/sustainable protection. In fact, progesterone, but not MPA, increased the expression of the anti-apoptotic Bcl-2 protein. And as observed in the model of glutamate-induced Ca^{2+} influx, MPA not only failed to increase expression of Bcl-2, but actually inhibited that elicited by estradiol (Nilsen and Brinton, 2002a).

The disparity between the effects of progesterone and MPA has also been observed *in vivo*. For example, a study using rhesus monkeys illustrated that combined treatment with estradiol and progesterone protects against coronary vasospasm, whereas estradiol + MPA treatment did not (Miyagawa et al., 1997). And once again, in contrast to the antagonistic effects of MPA on estrogen's effects, progesterone enhanced the protective effects of estrogen against exercise-induced myocardial ischemia in post-menopausal women, whereas MPA did not (Rosano et al., 2000). Moreover, in a model of stroke (reversible focal stroke using the intraluminal filament model followed by 22 h of reperfusion), MPA diminished the protective effects of conjugated equine estrogens (CEE) and MPA diminished estrogen's ability to reduce stroke damage. The functional antagonistic effects of MPA were also noted in the cholinergic system of monkeys, where MPA administered in conjunction with CEE reduced choline acetyl transferase (ChAT) in such cognition-relevant areas of the brain as the medial septum (Gibbs et al., 2002). Similar consequences of MPA were seen in the cardiovascular system of cynomolgus monkeys. Adams et al. (1997), demonstrated that monkeys treated with CEE showed a 72% reduction in coronary artery atherosclerosis whereas there were no benefits observed in CEE plus MPA group. Interestingly, with regards to the traumatic brain injury model, MPA required a larger dose than progesterone to accomplish a comparable reduction in cerebral edema. However regardless of the dose of MPA, MPA did not favor a better behavioral recovery than progesterone (reviewed in Stein, 2005). A summary of the comparison between the potentially neuroprotection-relevant effects of progesterone and MPA are provided in Table 1.

Collectively, the information presented here supports the conclusion that progesterone is protective and that such protection can be afforded through multiple mechanisms. In addition, the data from several laboratories support the conclusion that not all progestins are created equal, particularly within the context of neuroprotection. Such differences may be important in considering the results of the WHIMS studies which used MPA rather than progesterone, and further, could provide critical insight into the development of the most effective therapeutic formulations for the treatment of the menopause and various diseases whose incidence increases during the post-menopausal period.

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