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# Progesterone-induced Neuroprotection: Factors that may predict therapeutic efficacy

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## Abstract

Both progesterone and estradiol have well-described neuroprotective effects against numerous insults in a variety of cell culture models, animal models and in humans. However, the efficacy of these hormones may depend on a variety of factors, including the type of hormone used (ex. progesterone versus medroxyprogesterone acetate), the duration of the postmenopausal period prior to initiating the hormone intervention, and potentially, the age of the subject. The latter two factors relate to the proposed existence of a "window of therapeutic opportunity" for steroid hormones in the brain. While such a window of opportunity has been described for estrogen, there is a paucity of information to address whether such a window of opportunity exists for progesterone and its related progestins. Here, we review known cellular mechanisms likely to underlie the protective effects of progesterone and furthermore, describe key differences in the neurobiology of progesterone and the synthetic progestin, medroxyprogesterone acetate (MPA). Based on the latter, we offer a model that defines some of the key cellular and molecular players that predict the neuroprotective efficacy of progesterone. Accordingly, we suggest how changes in the expression or function of these cellular and molecular targets of progesterone with age or prolonged duration of hormone withdrawal (such as following surgical or natural menopause) may impact the efficacy of progesterone.

Progesterone, like estrogen, is a gonadal steroid hormone that has classically been associated with reproductive function, and accordingly, most of the literature related to progesterone and the brain focuses on the hypothalamus as the relevant target. However, extra-hypothalamic functions of these steroids are now also apparent. Certainly, the widespread expression of receptors for progesterone and estrogen would support the broader scope of gonadal hormone action, and such diversity of function is underscored by the ability of gonadal hormones to regulate neurite outgrowth and differentiation (Toran-Allerand, 1976; Toran-Allerand, 1980), survival, plasticity and regeneration (Behl et al., 1995; Matsumoto and Arai, 1981; Simpkins et al., 1997), and also the ability to modulate cognitive function (Luine et al., 1998; Singh et al., 1994).

With age, circulating gonadal hormone levels decline in both males and females. In women, however, such age-associated decreases are much more dramatic as a result of the



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menopause. The menopause occurs at an average age of 51 (Source: National Institute on Aging), and is characterized by a precipitous decline in circulating gonadal hormones. Since the average lifespan of women has increased to approximately 80 yrs of age (U.S. National Center for Health Statistics, National Vital Statistics Reports (NVSR), *Deaths: Final Data for 2007*. Vol. 58, No. 19, May 2010), a substantial portion of a woman's life is spent in a hormone-deprived state. Given that many neuronal and glial cell populations are normal targets of hormones such as progesterone, it is critical to address the impact of this age-related hormonal decline on brain function. Further, the rather glaring discrepancy between numerous basic (bench) science, epidemiological and clinical studies that documented the protective effects of gonadal hormones on brain structure and function, and the results from the Women's Health Initiative (WHI), warrant clarification. In fact, these contrasting results underscore our limited understanding of the neurobiology of these hormones. One hypothesis that has emerged to reconcile some of the basic (bench) research with the results of the WHI is that there exists a "critical window" of therapeutic opportunity for gonadal steroid hormones (Bohacek and Daniel, 2010; Daniel and Bohacek, 2010; Dunkin et al., 2005; Henderson, 2006; Pinna et al., 2008; Sherwin, 2005; Smith et al., 2010; Suzuki et al., 2007; Wu et al., 2011; Zandi et al., 2002). While such a window of opportunity has been described for estrogen, it is still relatively unclear if such a window of opportunity exists for progesterone and its related progestins. In this review, we summarize data from our laboratory and that of others that describe the various mechanisms underlying progesterone-induced brain protection, and further, through our current understanding of key differences in the neurobiology of progesterone and the synthetic progestin, medroxyprogesterone acetate (MPA), offer a model that defines some of the key cellular and molecular players that predict the neuroprotective efficacy of progesterone. Accordingly, we suggest how changes in the expression or function of these cellular and molecular targets of progesterone with age or prolonged duration of hormone withdrawal (such as following surgical or natural menopause) may impact the efficacy of progesterone. We suggest that a better understanding of the regulation of these cellular mediators of progesterone-induced protection could yield insight into the extension of the therapeutic window of opportunity.

## 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; Nilsen and Brinton, 2002b; Nilsen and Brinton, 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.* 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. 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 hours after injury (Roof et al., 1996). 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.* 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). 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; Gonzalez Deniselle et al., 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).

## 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, can promote cell survival. Alternatively, progesterone may act through novel receptor systems, such as a

membrane associated progesterone receptor 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 (Singh and Su, 2012; Su et al., 2012b). 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, 2002a; 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, 2002a; Nilsen and Brinton, 2003) but has also been shown to depend on the activation of these pathways (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, 2002a).

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 (see (Deutsch et al., 1992) for review). 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; He et al., 2004b; Sayeed et al., 2009; Vitarbo et al., 2004). In addition to the effects of allopregnanolone on the GABAA 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 GABAA receptor. Progesterone may influence the GABAA 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 GABAA receptor (Bell-Horner et al., 2006; Vasan et al., 2003). Since the regulation of the GABAA receptor has been shown to modulate cell survival, particularly in models of excitotoxicity, the regulation of the GABAA 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).

## 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 and colleagues (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., describe the key role of the classical PR in neuroprotection after experimental stroke (Liu et al., 2012), 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; Balasubramanian et al., 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 seven transmembrane-spanning domain, and is coupled to the Gi/o class of G-proteins (Zhu et al., 2003b). Other membrane progesterone receptors include 25-Dx (also called Pgrmc1) (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 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 (Su et al., 2012a). Further, this effect on BDNF release appears to be mediated by ERK5 (Su et al., 2011; Su et al., 2012a). As such, 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), an effect that appears to be mediate by a membrane receptor other than Pgrmc1 or the classical PR (Su et al., 2012a), and is yet 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 (σ1) receptor (Selmin et al., 1996; Seth et al., 1998). Given the reported role of the sigma 1 receptor in neuroprotection (for review, see (Maurice et al., 2006)), this mechanism may also be relevant to progesterone's protective actions.

## The neurobiology of progesterone versus medroxyprogesterone acetate

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 un-opposed 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 actually suggest that it 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, 2002b). Furthermore, while some of the neuroprotective effects of progesterone are mediated by its neuroactive metabolite, allopregnanolone (see discussion above), it is unclear if MPA is a substrate for the progesterone metabolizing enzymes 5alpha-reductase and 3alpha-hydroxysteroid dehydrogenase. If anything, MPA has 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, 2002b; Nilsen and Brinton, 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 (Nilsen and Brinton, 2002a). 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, 2002b).

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 to, 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 hours of reperfusion), MPA diminished the protective effects of conjugated equine estrogens (CEE) and MPA diminished estrogen's ability to reduce stroke damage (Littleton-Kearney et al., 2005). 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., 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 (Adams et al., 1997). 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)).

## Progesterone's protective effects are influenced by age

Unfortunately, there is very limited information on how the cytoprotective effects of progesterone are altered with age. A few studies have, however, suggested that progesterone protective effects are diminished with age. For example, in one study progesterone significantly reduced the experimental stroke-induced lesion volume in young adult (3 month old) ovariectomized (OVX) C57Bl/6 mice, but had no effect on neurological outcome in older (12 month old) OVX mice (Gibson et al., 2011). Further, recent data from our laboratory suggests that while progesterone increased BDNF expression in the hippocampus of young adult rats (4 months of age), the response of the hippocampus of older (10 month old) mice was significantly reduced (Singh, Su, Yang, Sumien and Forster, unpublished data). Given the implicated importance of neurotrophin signaling in the protective effects of progesterone, we suggest that deficits in capacity of progesterone to promote the synthesis and availability of neurotrophins to other cells may underlie, at least in part, this diminished response with age.

## The biological basis for a window of opportunity for progesterone

Based on the mechanistic differences between progesterone and MPA that our lab and others have described to explain why progesterone is protective but MPA is not, we propose that the biological basis for a window of opportunity for progesterone may, in part, be influenced

by: 1) the relative expression, binding activity and distribution of the certain progesterone receptors in the brain and, 2) potential changes in neurotrophin regulation and it's associated signaling cascades coupling progesterone receptors and their downstream targets.

Given the importance of BDNF as a cellular mediator of progesterone-induced brain protection (Kaur et al., 2007), and the role of the PR and Pgrmc1 in mediating the effects of progesterone on BDNF synthesis and release (Su et al., 2012a), respectively, we suggest that the complementary actions of membrane and intracellular progesterone receptors are required to afford protection. Given that the classical progesterone receptor is necessary for the induction of BDNF synthesis, but a membrane-associated progesterone receptor (Pgrmc1) is required for progesterone-induced release of BDNF, we propose that the two must act in tandem for protection to be afforded. As such, a decline in the expression of either the PR or Pgrmc1 would contribute to a diminished response to progesterone, within the context of cytoprotection, and thus, implicate these two receptors in defining a therapeutic window of opportunity. Alternatively, since the protective effects of progesterone are noted to depend on neurotrophin signaling, including activation of the ERK/MAPK or PI3K/Akt signaling pathways, a change in the relative expression of the neurotrophins, their cognate receptors (Trk receptors) or specific signaling proteins may similarly impact the capacity of progesterone to promote brain health. Supporting the latter is the observation of an age-related decrease in ERK1/2 activity in the rat dentate gyrus (McGahon et al., 1999) and cerebral cortex (Zhen et al., 1999).

While a finite window of therapeutic opportunity for estrogens in the aging brain have been defined to some extent, along with some of the mechanisms to explain the altered response of the brain to estrogens with age, we are unaware of any published data that addresses whether such a limited window of opportunity for progesterone (or its related progestins) exists. Recent data from our laboratory support the conclusion that there does, indeed, exist an age-associated loss of sensitivity of the brain to progesterone (at least with respect to the regulation of BDNF expression). Further, we believe that the data from mechanistic studies aimed at explaining the difference in neuroprotective efficacy between progesterone and MPA offer unique insight into the mechanisms that may be required for progesterone to elicit protective effects, and as such, provide a basis for explaining a potentially limited window of opportunity of therapeutic efficacy for progesterone. Future studies, from our laboratory and others, will undoubtedly provide more clarity to this important topic and consequently has the potential to help refine the future of hormone therapy.

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