The Case for Progesterone

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ABSTRACT: Recent clinical trials in hormone therapy (HT) for women approaching or past menopause have been disappointing. Most women who have been taking conjugated equine estrogens combined with synthetic progestins have been encouraged to stop these supplements because of increased health risks. The results of the clinical trials may be accurate about the risks associated with the synthetic compounds and combinations, but the data do not reflect what might have been the case if 17β-estradiol had been tested with natural progesterone instead of synthetic medroxyprogesterone acetate. For the most part, in almost all work on HT, estrogens have been given the primary focus despite the fact that progesterone has important properties that can enhance the repair of neurodegenerative and traumatic injuries to the central nervous system. This article reviews some of those properties and discusses the evidence suggesting that, if HT is to be reconsidered, progesterone should be given more attention as a potent neurotrophic agent that may play an important role in reducing or preventing motor, cognitive, and sensory impairments that can accompany senescence in both males and females.

KEYWORDS: progesterone; neurosteroids; hormone therapy; menopause; aging; brain damage; recovery

THE CASE FOR PROGESTERONE

It may seem strange to talk about "the case for progesterone" in the context of a meeting about the *future* of estrogen and hormone therapy in postmenopausal women, which is the title of the conference on which this book is based. The conference brought together leading neuroendocrinologists to discuss the controversy and need for future research generated by the recently terminated Women's Health Initiative (WHI) clinical trials on the risks and benefits of estrogen therapy (ET) and hormone therapy (HT). These trials,

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started in the mid-1990s, had multiple objectives: to examine whether estrogen alone or estrogen combined with the synthetic progestin, medroxyprogesterone acetate (MPA), would (1) reduce the incidence of dementias and cognitive impairments in post-menopausal women; (2) reduce the incidence of stroke, deep vein thrombosis, and heart disease; (3) decrease hip fractures; and (4) affect the risk of developing certain kinds of cancers (e.g., uterine, endometrial, colorectal, breast).

Unfortunately for millions of women on HT, the trials were terminated because the results reportedly showed that the treatments did not reduce the incidence of stroke or dementia, and indeed women taking HT had more strokes than those taking placebos. On the positive side, there were data indicating slightly fewer hip fractures and slightly fewer incidents of breast cancers (e.g., of 10,000 women on HT, "possibly 7 had fewer breast cancers"). However, the report[1] concluded that "Overall health risks exceeded benefits from the use of combined estrogen plus progesterone in healthy, postmenopausal women … and the regimen should not be initiated or continued for primary prevention of coronary heart disease ..." (p. 321). In a review of clinical trials in stroke, Brass reported that three separate trials failed to find any benefits of estrogen alone or in combination with synthetic progestins in preventing the first occurrence of a stroke or in reducing the risk of a recurrent stroke.[2] Subsequent briefings issued on behalf of the WHI investigators reported that HT was also "ineffective in protecting against deep vein thrombosis or cognitive impairments, memory problems and dementia."[1]

The articles in this volume on the future of estrogen in hormone therapy in women will supply many important facts and a variety of perspectives on the question of whether the clinical trials effectively evaluated estrogen's role in women's health as they approach and pass through menopause. Yet the whole issue of whether HT is effective or even risky has been only partially addressed, because the WHI study tested only women who were receiving conjugated equine estrogens, either alone or combined with MPA, rather than the natural forms of these hormones. There is growing evidence that the receptor and molecular actions of these agents could be quite different (see the chapter by Dr. R.D. Brinton and the following discussion for more examples).

Why might it be worthwhile to examine whether natural progesterone confers beneficial effects on its own, rather than as an adjunct used primarily to offset the risks of taking unopposed estrogen as preventive treatment against certain health risks in older women? One important consideration is that the progestagenic component of HT may have played a significant role in the outcome of the WHI's clinical studies, a topic that appears to be not only generally underdiscussed but also underrepresented in the literature. It is my contention that we need more study of whether reevaluation of HT is in-order—with different formulations and combinations of sex hormones that take advantage of the beneficial effects of progesterone in reducing the risk

of cognitive disorders and dementia in both men and women. Independently of HT and menopause, there is considerable research on estrogen and progesterone showing that these steroids can shape and influence brain morphology and plasticity across the developmental spectrum.[3,4] There is also a substantial body of literature showing that both progesterone and estrogen can have dramatic, beneficial effects in the repair and regeneration of the damaged central nervous system (CNS).[5,6] What is learned about the role of the hormones in CNS plasticity and repair may also be relevant to the metabolic and structural changes in the aging brain and the effects of these changes on mood and cognitive performance.

Because my own field is recovery from brain damage, I will briefly review the growing literature demonstrating that *natural* progesterone may be a potent neuroprotective agent, especially in the treatment of traumatic brain injury (TBI), stroke, and certain neurodegenerative disorders. I contend that progesterone may be a better alternative to estrogen in the treatment of CNS injuries, but I also emphasize that a definitive claim must be based on more research. I want to make clear at the outset that most of my research over the last 15 years has focused on the role of progesterone in the experimental treatment of TBI, and more recently in an animal model of stroke. In our models of brain injury, treatments have always been given *after* damage has occurred, whereas in HT, the hormones have been administered as prophylactic agents to otherwise healthy women in the hope of reducing the risk of later disease. One important question to address is whether progesterone and its metabolites would compare favorably to estrogen in the reduction of risk for stroke and dementia for *both males and females*. In fact, this may turn out to be the major advantage of progesterone—which, unlike estrogen, can be given to both males and females without affecting gender and sexual functions.[a] Given the concerns over chronic estrogen administration, a second question, perhaps more critical to the issue of HT, is whether what we learn about the role of progestins in treating brain injury *after it occurs* is applicable to hormone replacement given prophylactically to essentially healthy pre- and postmenopausal women.

There are some interesting, rather unfortunate parallels between HT and TBI treatment research. In both fields, recent large-scale clinical trials had to be terminated because of negative outcomes. In the treatment of TBI, for the past 30 years, the most widely used early treatment to stop brain swelling and inflammation was the administration of relatively high doses of the glucocorticosteroid hormone methylprednisolone (Prednisone), but although this potent hormone was commonly used, it was never fully tested in a randomized clinical trial until recently. Then, under the auspices of the British Medical Research Council, a worldwide clinical trial was planned to test more than

[a]This limitation may change as nonfeminizing estrogens become available for clinical application, however.

20,000 brain-injured patients eligible for steroid treatment—half would be provided with the hormone and half would be given state-of-the-art treatment, but no Prednisone. After 10,000 subjects had been examined, it was found that at 2 weeks postinjury, the patients on the steroid had a substantially increased rate of death compared with control subjects. The trials were abruptly terminated.[7] This now leaves the victims of TBI, like the HT candidate population, with no acute-stage neuroprotective treatments to prevent the secondary loss of vulnerable brain cells. Enter progesterone (and perhaps estrogen?).

Until now, about 81% of papers using animal models of stroke focused exclusively on the neuroprotective effects of estrogen, with no direct comparisons to the progestins.[8–13] Despite the problems with the WHI clinical trial outcomes, it is not my intention to dispute the potential beneficial effects of unopposed estrogen treatments in animal models of stroke and other forms of neural injury such as retinal degeneration or spinal cord damage. I simply wish to propose here that the study of progestins as potential therapeutic agents in their own right deserves more consideration—if for no other reason than to definitively rule out any beneficial role they may play in HT or in repair of neural injuries. The issues can be formulated as two questions: (1) is there evidence that progesterone or its metabolites can enhance cognitive performance in intact subjects? and (2) do progesterone or its metabolites enhance recovery after injury to the brain?

DOES PROGESTERONE INFLUENCE MOOD, COGNITION, AND MEMORY IN HEALTHY SUBJECTS?

The literature surrounding progesterone's influence on mood, cognition, and memory in healthy subjects is not very large and not completely consistent, but in general it seems that both circulating levels and progesterone supplementation may be beneficial rather than detrimental in animals and humans. In one study, Hampson and Kimura[14] tested women (20–39 years old) on a battery of psychological tests during the early stages of their menstrual cycle (days 3–5) and then 7 days prior to menstrual onset. They found that on the tasks where women typically do better than men (mostly manual skills), performance was better during the midluteal phase, when progesterone levels are higher. Interestingly, on a perceptual task in which men typically excel, women were worse during the midluteal phase than they were during the menstrual phase of the cycle. This finding could be interpreted to mean that circulating levels of hormone may be beneficial to some aspects of performance, while not so good for other aspects. The Hampson and Kimura findings were disputed in a later study by Epting and Overman,[15] who examined both women and men on a similar variety of cognitive and motor tasks

but found no evidence that menstrual cycle affected performance.[b] As mentioned, findings in this area continue to be inconsistent and controversial (much like the work on estrogen). Recently, Solis-Ortiz, Guevara, and Corsi-Cabrera[16] examined nine healthy females with regular menstrual cycles on a cognitive test designed specifically to measure "executive functions" thought to be mediated by the prefrontal cortex (the Wisconsin Card Sorting Task, which measures abstract reasoning, problem solving, and working memory) while simultaneously recording EEG activity during ovulation, early luteal, late luteal, and menstrual phases of the cycle. Performance on the WCST was best during the early luteal phase when progesterone levels were highest, and there were no changes in EEG reactivity (compared with baseline at rest) during this phase. The changes seen in the forms of EEG activity were associated with lower levels of anxiety possibly caused by the higher levels of progesterone. The authors conclude that "high physiological progesterone levels as in early luteal phase favor performance of tasks demanding internal attention and planning" (p. 1054).

However, some cognitive problems that have been attributed to progesterone could be due to the fact that the hormone and its metabolites bind to GABA-A receptors and can produce temporary sedative-like effects, which may be influencing performance when subjective reports of fatigue and somnolence are strong. Women taking synthetic progesterone in combination with conjugated equine estrogens often report that they feel sleepy, groggy, or irritable shortly after taking progesterone, but this could be due to the dose (amount, hormones taken together or separately with a delay between estrogen and progesterone, and type of progestin—natural or synthetic). Several recent studies of progesterone's effects on sedation and motivation[17,18] found that single, relatively high, doses (100–200 mg, by intramuscular injection) given to small samples of men and pre- and postmenopausal women did lead to a mild increase in feelings of sedation and fatigue that was more prominent in the men, but there were no detrimental effects on memory or long-lasting effects on psychomotor performance. Even if mild sedative effects were obtained with doses of progesterone much higher than circulating levels in the luteal phase of the cycle, the hormone could be taken at night, before bedtime, when it might even improve sleep. In any case, the subjective feelings of fatigue and mild sedation following progesterone administration would seem to present less risk than some of the negative effects attributed to chronic estrogen administration. From my reading of this literature, small sample sizes and difficulties in defining the phase of the cycle, combined with the considerable variability in testing human subjects, has made interpretation of the usefulness of progesterone more complex than in laboratory animal studies.

[b]Epting and Overman[15] provide an informative brief discussion of problems and pitfalls in correlating menstrual cycle with psychological performance that might be helpful to those not expert in this field.

In laboratory animals, one way to examine the role of progesterone (and estrogen) in learning is to study females across the estrous cycle (or who have been ovariectomized) and determine whether any changes in performance correlate with metabolic and/or structural changes in the brain.[c] About 8 years ago, Warren and Juraska[19] examined adult male and female rats in a spatial learning task considered to be sensitive to hippocampal "function." The females were subdivided into three groups according to their phase of the estral cycle (proestrus, estrus, and diestrus). These investigators found that performance of the females varied according to both the specific demands of the task *and* where they were in the estrous cycle, "with females in the estrus phase, when estrogen is low, outperforming those in the proestrus phase on place learning" (p. 263). In other words, the females appeared to do better when they were lower in estrogen, despite the fact that estrogen was reported to enhance synaptic density thought to be beneficial in complex spatial learning. The authors conclude: "Although inconsistent with traditional views of the relationship between synapse density, [long-term potentiation], and spatial memory, [their findings] are consistent with previous reports that spatial memory is better in females when estrogen is low" (p. 265). As with the human literature, the data need to be interpreted cautiously because of inconsistent results. For instance, Chesler and Juraska[20] also reported that when estrogen or progesterone were given separately to ovariectomized rats, there were no impairments relative to age-matched control subjects on a spatial learning task thought to be mediated by hippocampal activity. However, when the two hormones were given together, there was a deficit in the acquisition of place learning strategy. Here the *combination* of higher steroid levels was detrimental. The authors also suggest that their results have implications for other hormone replacement studies using chronic doses that do not mimic the transient fluctuations typical of the natural release of the hormones, or have withdrawal effects, both of which could modify behavioral outcomes (this could also be an important factor in the behavioral outcome measures in the human HT trials). To complicate the issue even further, the Juraska group recently showed that the effects of the estrous cycle on spatial learning can be dependent on the temperature of the water used in the Morris water maze.[21] Proestrous rats performed better when the water was relatively warm, whereas the rats in estrus performed

[c]The hippocampus has received particular attention in this context because cellular electrophysiological changes in long-term potentiation (LTP) play a role in memory formation. *See* M.R. Mehta (2004), Cooperative LTP can map memory sequences on dendritic branches, Trends Neurosci **27:** 69–72; M.A. Lynch (2004), Long-term potentiation and memory, Physiol. Rev. **84:** 87–136; S.J. Martin & R.G. Morris (2002), New life in an old idea: the synaptic plasticity and memory hypothesis revisited, Hippocampus **12:** 609–636; and, because LTP is also correlated with alterations in dendritic and synaptic morphology, C.S. Woolley & B.S. McEwen (1992), Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat, J. Neurosci. **12:** 2549–2554.

better in cold water. These effects may well have been mediated by the rats' response to a stressful situation (with cold water taken to be more stressful than warm), but it also emphasizes how results could vary between labs and how the differences in "task variables" could affect the interpretation of findings—and illustrate why, in the human studies, clinical trial outcomes can be so variable and require such large numbers of subjects before any substantive conclusions can be drawn.

Galea *et al.*[22] also used rats to investigate the effects of pregnancy on spatial learning performance and volume of the hippocampus. In general, the pregnant females showed much better performance in two spatial learning tasks (involving acquisition and working memory in the Morris water maze) than their nonpregnant counterparts, especially in weeks 1 and 2 of gestation, when progesterone levels were at their highest. The animals were worse during the third trimester, when estradiol was highest. The authors took their results to mean that high levels of estrogen can inhibit spatial learning and memory and that progesterone may be beneficial to the process. They state that the results of their study "point to a potential facilitatory role of progesterone on performance" (p. 93). They hypothesize that the decrease in spatial learning ability in the third trimester keeps the rats closer to the nest at the time when they need to be concerned with building a nest, preparing for parturition, and avoiding predators. Hippocampal volumes were not affected by pregnancy versus nonpregnant control subjects.

About a decade ago, a group from Mexico[23] reported that females in estrus were impaired on the acquisition of a conditioned avoidance response. This task requires animals to learn to inhibit their activity upon hearing a tone in order to avoid footshock and can be considered stressful. Progesterone administration enhanced learning of the task when given to rats in estrus, but not at diestrus, suggesting an interaction between the two hormones in mediating this response to a stress-learning situation. Gibbs[24] has also shown that, relative to age-matched nontreated animals, long-term treatment combining estrogen *and* progesterone will enhance spatial memory learning in aged, ovariectomized rats. Animals given estrogen alone did better on the learning task than the placebo group but were not as good as rats given both progesterone and estrogen therapy; this latter group outperformed all others in the study. If treatments were started within 3 months of the ovariectomies, the performance outcomes were better than if the hormone treatments began 10 months after surgery. Gibbs argues[24] that the hormones enhance learning and memory by increasing levels of cholinergic neurotransmitters in the hippocampus, frontal cortex, and nucleus basalis magnocellularis (NBM)—parts of the brain that contain progesterone receptors and which are strongly implicated in mediating learning and memory. Thus, the improved performance in the aged rats may be due not only to the anxiolytic, GABAergic, calming effects of long-term exposure to progesterone but also to its effects on cholinergic (activational) mechanisms.

A recent report by Bimonte-Nelson *et al.* suggests that the role of progesterone in aged female rats needs to be clarified even further.[25] This group had previously reported that ovariectomy in aged rats improved performance in a spatial learning task, which is the opposite of what is found when young animals are subjected to this procedure. They point out that in old females progesterone levels remain high relative to estrogen (pseudopregnant estropause), so removals of the ovaries reduce the levels and lead to better performance in the old rats. In this study, progesterone supplementation had a negative effect on cognition and working memory. It is hard to reconcile these diverse findings. Dose, timing of administration (early or later after ovariectomy), hormonal and metabolic status of the brain at time of administration, interactions with estrogen dose, maze water temperature, strain of the rats tested, etc., could account for the conflicting results. Clearly some standardization in methodologies will be required before the specific role of progesterone in hormone supplementation can be understood. In light of the failure of the WHI, HERS, and other clinical trials, it becomes particularly pressing to examine these issues if HT is to be reconsidered.

DO PROGESTERONE OR ITS METABOLITES ENHANCE RECOVERY AFTER INJURY TO THE BRAIN?

Unlike the HT/supplementation research, studies using animal models of TBI and stroke more consistently demonstrate that progesterone has beneficial effects. From several studies, we now know that natural progesterone given to both males and females (1) can easily cross the blood–brain barrier (BBB)[26] and dramatically reduce edema to barely measurable levels in the injured animal brain[27,28]; (2) can reduce lipid peroxidation and the generation of isoprostanes, which in turn contribute to postinjury ischemic conditions[29]; (3) protects neurons distal to the site of injury that would normally die after TBI[30]; (4) produces significant sparing of cognitive, sensory, and spatial learning performance in laboratory rats after bilateral injury of the medial frontal cortex (MFC)[30]; generates metabolites that (5) reduce proapoptotic and increase antiapoptotic enzymes[31] and (6) reduces the expression of proinflammatory genes and their protein products[32]; (7) enhances oligodendrocyte-induced remyelination in young and aged rats with demyelinating disorders[33,34]; (8) produces effects repeatable across species (both mice and rats) with comparable effective doses[35,36]; and (9) as shown in the work of other groups using two different models of cerebral ischemia, significantly reduces the area of necrotic cell death and improves behavioral outcomes.[37]

In senescent subjects of both sexes, there are lower levels of circulating steroids, and this could affect the organism's capacity to respond adaptively to TBI. The systemic administration of progesterone to these subjects could

have substantial effects on both the immune response to brain injury and the neural repair mechanisms associated with behavioral recovery. With reproductive senescence in female rats, investigators have shown that there is a loss of "intrinsic" neuroprotection after ischemic injury (premenopausal females tend to have better recovery outcomes than males),[38] but with replacement of both estrogen and progesterone the size of the infarcts was significantly smaller.[39] Although promising for females, a study by Alkayed *et al.* did not examine whether similar progesterone treatments would be as effective in senescent males.[39] There is little else to report on the use of neurosteroids in aged, brain-damaged subjects, with the exception of a few studies suggesting that treatment with progesterone could be successful in other diseases/disorders related to TBI outcomes in aged subjects.

Gangula *et al.*[40] reported that hypertension morbidity increases in postmenopausal females when hormones like progesterone and estrogen are depleted. This can be reversed after neurosteroid administration. This study also found that progesterone regulates the effects of calcitonin gene–related peptide (CGRP), a potent vasodilator. The hypotensive effects of CGRP were significantly enhanced in the presence of estrogen or progesterone treatments in both aged and younger female rats. Obviously, the control of blood pressure in old subjects could play a role in the cascade of injury events following a TBI and needs to be examined after progesterone treatment in the elderly. As noted earlier, Gibbs recently reported that aging, combined with loss of ovarian function, causes substantial reduction in ChAT and trkA mRNA in the medial septum and nucleus basalis relative to younger animals.[41]

Progesterone's effects on the aging nervous system have also been reported by Azcoitia *et al.* and by Ibanez *et al.*,[33,42] who found that supplementary progesterone promotes the expression of myelin proteins in the damaged sciatic nerves of young adult rats and in 22–24-month-old males with nerve crush injuries. Ibanez *et al.* took this work further and studied whether treatment with progesterone in young and aged rats enhances remyelination in the brain itself after damage to brainstem white matter. Although the process of repair took longer in the aged rats, treatment with progesterone doubled the expression of myelin seen in the aged control subjects. In mature animals, progesterone substantially reduces injury-induced cytotoxic and vasogenic swelling and leads to enhanced morphological and behavioral recovery after TBI in young adult animals. In a clinical trial at Emory, there have been no adverse events attributed to progesterone treatments in 100 patients with moderate to severe blunt head injury (average age, 39).[d]

We have previously shown that contusion injury to the MFC in young adult rats causes severe deficits in the acquisition of a spatial learning task in the Morris water maze.[43] Damage to the frontal cortex will also produce enduring bilateral sensory neglect of the forelimbs and tongue.[43,44] In our studies,

[d]As of this writing the results of the double-blind trial have not yet been decoded.

5 days of postinjury treatment with progesterone significantly improved spatial learning and sensory performance compared with injured, untreated counterparts. In a recently published dose-response study,[35] we showed that the optimal dose of progesterone to promote cognitive recovery lies between 8 mg/kg of body weight and 16 mg/kg. In addition to the neuronal loss, the injury-induced disruption of the BBB has been associated with vasogenic edema. In our injury model there is severe damage to the vasculature with concomitant disruption to BBB integrity.[45] Progesterone reduces the permeability of the BBB to macromolecules but not to sodium ions *in vivo*,[46,47] and there is growing evidence to suggest that this neurosteroid also alters the function of aquaporins 4 and 9 in astrocytes, thus regulating swelling and water exchange.[48–50] We found that progesterone reduces Evans blue extravasation after cortical contusion,[51] suggesting that the neurosteroid plays a role in reconstituting the BBB, and we take this as indirect evidence that progesterone could be altering aquaporin function in the CNS.

Neurologists and neurosurgeons often stress the fact that "brain edema accounts for much of the morbidity and mortality associated with common neurological conditions such as head trauma, brain tumors, stroke, and liver failure."[52] Vasogenic edema occurs when the BBB is compromised and plasma fluid enters the brain parenchyma. Cytotoxic edema occurring somewhat later than the vasogenic variety is caused by accumulation of fluid within the brain cells themselves. In particular, reactive astrocytes take up fluid and then cause further damage because they cannot participate in repair mechanisms and homeostasis. One of the major beneficial effects of progesterone is that it substantially reduces both vasogenic and cytotoxic edema after TBI.[51] In the model of middle cerebral artery occlusion (MCAO), progesterone reduced tissue water content significantly.[46] In a neurogenic model of cerebral edema, both progesterone and allopregnanolone reduced plasma extravasation.[53] In our laboratory, following bilateral contusions of the MFC, brain water content was significantly reduced in pseudopregnant females, in ovariectomized females given progesterone, and in males given injections of progesterone.[27,54,55] Progesterone was able to reduce cerebral edema even when treatment was delayed up to 24 hours after injury.[27]

Although progesterone does not have the characteristic structure of an antioxidant, high endogenous levels of, or exogenous treatments with, this hormone are effective in reducing free radical damage.[56–59] Pregnancy itself can reduce lipid peroxidation in brain homogenates and mitochondria as measured by the thiobarbituric acid method.[56–59] Progesterone administration reduces lipid peroxidation in three different types of *in vitro* free radical-generating systems in a dose-dependent manner[58,59] and increases levels of mitochondrial glutathione, a critical free-radical scavenger enzyme.[58] A recent study demonstrated that progesterone protects mitochondrial function in neural cells *in vitro* after mechanical stretch injury.[60] Progesterone downregulated injury-induced increases in manganese super-

oxide dismutase.[61] Progesterone treatment results in less nitrite, superoxide, and hydrogen peroxide generated by cultured cytokine-stimulated macrophages.[62] Macrophages are known to be very active between 48 h and 7 days after TBI, and a reduction of these reactive cells can reduce secondary damage to neurons.[63–65] Following cortical contusions, rats given progesterone postinjury had significantly less 8-isoprostane, a vasoconstrictive free radical-generated prostaglandin, than untreated control subjects at 24 and 48 h postinjury.[57] Although it did not involve direct manipulation of progesterone levels, a recent study demonstrated that in very severely brain-injured females, prostaglandin levels are roughly half those seen in males with the same brain injury.[66] These studies suggest that progesterone reduces lipid peroxidation, most likely through a combination of a decrease in generation of free radicals and enhancement of endogenous free radical-scavenging systems.

In excitotoxic lesions *in vivo*, early (1–4 h) microglial expression of the proinflammatory cytokine interleukin 1β (IL-1) is seen in the area of the lesion, and later (24 h to 7 days in microglia and astrocytes) in areas of reactive gliosis.[67] Inhibition of IL-1 reduces the severity of injury induced by TBI or excitotoxicity.[67] Tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) can activate microglia *in vitro*, and progesterone will inhibit this microglial reactivity. Progesterone also decreases TNF-α, iNOS (protein and mRNA), and NO released by these microglia.[68] Recent evidence supports the notion that reactive astrocytes and microglia play a role in oligodendrocytic apoptosis and that TNF-α released in reactive gliosis is known to induce apoptosis.[69]

Our cortical contusion injury model produces a marked inflammatory reaction, with heavy gliosis seen in brain areas proximal and distal to the injury.[64] The frontal-cortical contusions lead to invasion of macrophages and neutrophils into the impact area with numbers that peak approximately 72 h after injury. This may be why 3–5 days of treatment with progesterone is more effective for behavioral recovery than a single injection.[63] In addition, heavy microgliosis and astrogliosis are present in both fascicles and nuclei with connections to the MFC—for example, the mediodorsal thalamus and the NBM.[43] Progesterone has been shown to reduce the response of natural killer cells as well as the expression of known initiators of inflammation, for example, complement factor C3, NFB, TNF-α, IL-6, IL-1, and myeloperoxidase activity.[70–72] The literature and this work both support the idea that progesterone reduces inflammatory immune response.[62,73–78]

To highlight the importance of the type of hormone used, we recently completed a study comparing 4, 8, and 16 mg/kg of the synthetic progestin, MPA in the treatment of cerebral edema following bilateral fronto-cortical contusions in adult male rats. Our data showed that 2 days after injury the animals given the highest dose of MPA had edema levels comparable to the reduced edema after treatment with 4 mg/kg of natural progesterone. The 8 mg/kg of

MPA also reduced edema but not to the level seen in the 16 mg/kg MPA or the 4 mg/kg of natural progesterone. Interestingly, unlike natural progesterone and regardless of the dose, the MPA did *not* enhance behavioral recovery, suggesting that the pathways of action of the two agents diverge. This is in some respects similar to the effects of methylprednisolone, which may reduce edema but ends up killing more patients than giving no steroid treatment.[7] Given the inconsistent findings on the molecular effects of MPA in the CNS of laboratory animals, further investigation of the differences or similarities between natural and synthetic progestins is critical for determining whether treatment with these two forms of the hormone is appropriate for administration in senescent males and females.

Progesterone administration has been shown to decrease the infarct area after MCAO in rats.[37] Accompanying this decrease were improvements in body weight and neurological outcome. Progesterone appears to be effective in treating acute global ischemia in cats.[79] In this injury model, there is a loss of 54%–85% of neurons in the CA1 and CA2 subfields. After pre- and posttreatment with progesterone in ovariectomized cats, neuronal loss was reduced to between 21% and 49%. Recently, Chen *et al.* have shown that progesterone can decrease sensory neglect and enhance sensorimotor performance after MCAO in the rat.[80] These findings have been confirmed in a recent series of studies by Gibson *et al.*[81] In a model of penetrating brain injury, progesterone significantly decreased the accumulation of astrocytes in the proximity of the wound and decreased bromodeoxyuridine incorporation, a marker of cell division in reactive astrocytes.[82,83]

Progesterone given to rats with spinal cord contusions reduced tissue loss at the epicenter of the injury. Tissue sparing was accompanied by better outcomes on the Basso–Beattie–Bresnehan locomotor rating scale at 6 weeks postinjury.[84] Baulieu and colleagues found that progesterone is needed for remyelination of the injured sciatic nerve.[85,86] Using a cryolesion technique, they increased remyelination by 25% over controls with local injections of progesterone or pregnenolone. Progesterone and its GABA-ergic metabolites have been known to have strong antiseizure actions, especially in relation to catamenial epilepsy in females. Currently, there are two NIH-funded clinical trials for the progesterone treatment of epilepsy in females.

Cerebral edema is often a major complication of head injury leading to further neuronal loss and severe disability or the death of head trauma victims.[87,88] We demonstrated progesterone's capacity to reduce postinjury brain edema and enhance functional recovery.[27,28,30,51,54,89] In both males and females, progesterone treatment after TBI improved spatial learning performance, dramatically reduced edema and subsequent neuronal degeneration, and restored the integrity of the BBB. Analysis of the temporal parameters of progesterone's action also showed that the window of opportunity for the reduction of edema was large (up to 24 h postinjury), making the timely administration of progesterone to head-injured patients feasible and practical.[27]

These results in combination form a complicated but very interesting picture. Obviously, both the human and animal literature on HT present conflicting results, and the reasons for some of these conflicts have been discussed in this short review. The work with progesterone in brain-damaged laboratory animals of both sexes and across different species is more consistent, but this may simply be due to the fact that the field is newer than HT research and there are fewer studies comparing and contrasting all the potential variables. What is important is that progesterone seems to have the potential to enhance neuronal repair, in both males and females, something that has not been studied as much compared to estrogen—for all the obvious reasons. Far less attention has been paid to progesterone's potential in its own right as a neuroprotective agent that might also reduce some of the heath risks associated with hormonal loss in aging and menopause. Whether the case for progesterone in HT deserves further study is a judgment each reader will have to make.

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