Does Progesterone Have Neuroprotective Properties?

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In this article, we review published preclinical and epidemiologic studies that examine progesterone’s role in the central nervous system. Its effects on the reproductive and endocrine systems are well known, but a large and growing body of evidence, including a recently published pilot clinical trial, indicates that the hormone also exerts neuroprotective effects on the central nervous system. We now know that it is produced in the brain, for the brain, by neurons and glial cells in the central and peripheral nervous system of both male and female individuals.

Laboratories around the world have reported that administering relatively large doses of progesterone during the first few hours to days after injury significantly limits central nervous system damage, reduces loss of neural tissue, and improves functional recovery. Although the research published to date has focused primarily on progesterone’s effects on blunt traumatic brain injury, there is evidence that the hormone affords protection from several forms of acute central nervous system injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury. Progesterone appears to exert its protective effects by protecting or rebuilding the blood-brain barrier, decreasing development of cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis. All are plausible mechanisms of neuroprotection.

OVERVIEW

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THE TREATMENT CHALLENGE

Throughout the past 20 years, a large body of research has enhanced our understanding of the pathophysiology of acute brain injury. The tissue damage and destruction caused by the initial trauma trigger deleterious processes in the brain that can progressively enlarge the area of injury, leading to death or a lifetime of disability. Pathophysiologic changes include release of excitatory amino acids, activation of the N-methyl-D-aspartate receptor, the influx of toxic levels of calcium into neurons, activation of proinflammatory cytokines, and other events. Discovery of this injury cascade gives scientists hope that it may be possible to block 1 or more points in this process and thereby limit the consequences of brain injury. Unfortunately, the goal of identifying an effective neuroprotective agent has proven elusive. To date, more than 30 pharmacologic agents have been tested in clinical trials. None has consistently improved outcomes after traumatic brain injury.
Beyond providing supportive care, including maintenance of cerebral perfusion pressure, and avoiding hypoxemia, there is little that physicians can do to alter the outcome of traumatic brain injury. In 1993, the Brain Trauma Foundation\textsuperscript{15} convened an international task force to review existing therapies and develop evidence-based guidelines for treatment. With the possible exception of mannitol and barbiturates, no agent was found to enhance recovery. Roberts et al\textsuperscript{16} reviewed 5 common traumatic brain injury treatments—hyperventilation, mannitol, cerebrospinal fluid drainage, barbiturates, and corticosteroids—and found that when studies were restricted to those with proper controls, none of these agents decreased morbidity or mortality after traumatic brain injury. Their discouraging conclusions are also reported in the Cochrane Library.\textsuperscript{17}

Despite substantial effort by the pharmaceutical industry, no new traumatic brain injury treatment has entered clinical practice in more than 30 years.\textsuperscript{16} One drug that was once a mainstay of treatment is now known to be harmful.\textsuperscript{17} The Corticosteroids After Significant Head Injury trial enrolled more than 10,000 subjects in 49 countries in an effort to conclusively demonstrate efficacy. The study was prematurely halted because the treatment group experienced a higher mortality rate than the control group.\textsuperscript{18} Recently, a National Institutes of Health–funded clinical trial of magnesium sulfate was terminated for the same reason.\textsuperscript{19} Hypothermia has produced promising results in some brain-injured subjects, but it may be harmful to older patients.\textsuperscript{20,21} The treatment remains investigational.\textsuperscript{22,23}

**PRECLINICAL RESEARCH**

**Traumatic Brain Injury**

In the late 1980s, while researching cerebral recovery after traumatic brain injury, Stein observed that female rats tended to recover better than males after an injury of identical severity.\textsuperscript{24} He devised a series of experiments to determine whether these outcome differences were real and, if so, whether they were due to structural dimorphisms between the brains of female and male rats or were a product of bioelectrochemical, receptor, or hormonal differences. Stein hypothesized that sex-related differences in brain injury have a hormonal basis and that the magnitude of recovery depends, at least in part, on where a female rat is in her estrus cycle at injury. To test these hypotheses, Roof et al\textsuperscript{25} used 3 groups of mature rats: males, cycling females in proestrus (when levels of estrogen are high but progesterone levels are at their nadir), and pseudopregnant females (when progesterone is elevated). Animals received a precisely calibrated contusion to the medial frontal cortex, an injury roughly analogous to a severe frontal lobe contusion in a human. Twenty-four hours after injury, the animals were killed. Samples of brain tissue from the area immediately surrounding the primary lesion were compared with same-brain control samples from an area remote from the injury. Analysis of the wet-to-dry tissue weights of these samples revealed that female rats in proestrus developed significantly less cerebral edema than male rats that had received the same injury. Pseudopregnant females, the group with the highest levels of progesterone, developed almost no postinjury cerebral edema (Figure 1).\textsuperscript{25}

To determine whether treatment with progesterone shortly after injury would produce similar effects, Stein’s team administered progesterone to male and female rats at 1, 6, 24, and 48 hours after a calibrated brain injury. Control animals of both sexes received the same injury, but were injected with peanut oil vehicle. Comparison of wet-to-dry tissue weights obtained 72 hours postinjury revealed that male and female rats treated with progesterone developed significantly less cerebral edema than vehicle-treated controls (Figure 2).\textsuperscript{26} Lesion volume and neuronal loss, the latter measured in the dorsomedial nucleus of the thalamus, were also significantly reduced.\textsuperscript{27} The treatment worked equally well in males and females, an important finding because at the time it was unclear whether male rats had active progesterone receptors in their brains.

Reduction of cerebral edema is important, but improvement of function is the ultimate goal of any neuroprotective drug. To determine whether progesterone improves recovery after traumatic brain injury, Stein’s team tested 4 groups of rats: brain-injured rats treated with progesterone, identically injured rats treated with placebo; uninjured sham-surgery controls + placebo, and uninjured sham-surgery controls + progesterone. Seven days later, all animals were tested with a Morris water maze, a spatial navigation task that measures a rat’s ability to learn the location of a platform.
postinjury cerebral edema is inversely related to the serum progesterone level (ie, the higher the progesterone level, the less edema). Goss et al demonstrated that efficacy follows a potentiating methylprednisolone increase glutamate toxicity in the brain by initiation. Another showed that the severity of treatment was initiated as late as 24 hours postinjury and still produce benefit, although the magnitude of effect was greater the sooner treatment was initiated. Stein’s group then sought to determine the optimal therapeutic window and duration of progesterone treatment. One study revealed that progesterone treatment could be initiated as late as 24 hours postinjury and still produce benefit, although the magnitude of effect was greater the sooner treatment was initiated. Another showed that the severity of postinjuiy cerebral edema is inversely related to the serum progesterone level (ie, the higher the progesterone level, the less the edema). Goss et al demonstrated that efficacy follows a U-shaped curve, depending on dose. The most effective doses were in the 8 to 16 mg/kg range; lower and higher (32 mg/kg) doses were less effective. Such U-shaped functions in dose-response studies are not uncommon. Cutler et al determined that dose tapering is important to prevent a “rebound effect” when progesterone treatment is abruptly withdrawn.

Because progesterone is classically defined as a steroid, it is logical to ask whether it is more effective than corticosteroids, a class of drugs used in the past to treat acute traumatic brain injury. Stein’s team found that progesterone is much more effective than methylprednisolone at reducing cerebral edema after traumatic brain injury. More recently, the Corticosteroids After Significant Head Injury trial determined that methylprednisolone treatment is deleterious in the setting of traumatic brain injury. Because steroids such as methylprednisolone increase glutamate toxicity in the brain by potentiating N-methyl-D-aspartate response and attenuating γ-amino butyric acid (GABA) response, it is not surprising that they are not neuroprotective. Conversely, progesterone reduces glutamate toxicity by decreasing its expression and by up-regulating GABA.

Although much early research on progesterone’s neuroprotective effects was conducted by Stein and colleagues, other groups have replicated these findings and added discoveries of their own. Asbury et al administered progesterone to rats shortly after bilateral medial frontal cortex aspiration and reported that treated animals had less neuronal loss in the mediodorsal thalamic nucleus and the striatum compared to untreated controls. In a rat model of penetrating brain injury, Garcia-Estrada et al determined that progesterone treatment decreases accumulation of astrocytes in the proximity of the injury. Several teams have independently reported that progesterone exerts beneficial effects in spinal cord injury, including enhanced remyelination and improved motor function. Vink and Van Den Heuvel reported that progesterone is effective in reducing the size of the deficit in rats with diffuse axonal injury after impact to the skull.

**Acute Stroke**

In the mid-1990s, researchers began to study whether progesterone limits the consequences of acute stroke. In most of these experiments, the animal’s middle cerebral artery is occluded for several hours and then allowed to reperfuse. In the first such experiment, Jiang et al administered progesterone at a dose of 4 mg/kg in dimethyl sulfoxide to male adult rats either immediately before middle cerebral artery occlusion or 2 hours after reperfusion. Regardless of which time was chosen, a single injection of progesterone resulted in significantly smaller cortical infarct volumes, less weight loss, and better neurologic outcomes compared to that of controls. Other teams replicated these findings.

Kumon et al reported that progesterone treatment improved neurologic outcomes and decreased cortical infarct size in normotensive and spontaneously hypertensive male rats. Morali et al reported that, in a stroke model, administering intravenous progesterone (8 mg/kg) to rats significantly reduced loss of pyramidal neurons in the cornu ammonis 1 and 2 fields of the dorsal hippocampus. Control rats given vehicle had a 2-fold increase in ventricular dilation and cerebral shrinkage. Recently, Sayeed et al reported that administering either progesterone or its metabolite, allopregnanolone, is beneficial in a temporary middle cerebral artery occlusion model of ischemic stroke. Sayeed subsequently replicated these findings in a rat model of permanent middle cerebral artery occlusion. In this study, 3 days of treatment with either progesterone or allopregnanolone produced markedly smaller necrotic infarcts and lower levels of cerebral edema compared to treatment with vehicle only.

**Other Neurologic Conditions**

Progesterone treatment may also be beneficial in demyelinating conditions such as multiple sclerosis. Schumacher et al reported that progesterone treatment of symptomatic Wobbler mice with motoneuron degeneration reduced neuropathology and up-regulated myelination in Schwann cells and oligodendrocytes in the central nervous system.
et al\textsuperscript{57} demonstrated that progesterone treatment increases myelin production, especially in injured animals. Similarly, Pascual et al\textsuperscript{66} reported that progesterone treatment can reverse the effects of hypoxic injury to the solitary tract nucleus of rats and thus rapidly enhance respiratory rhythms. The reaction was so rapid that the authors suggest it cannot be due to the traditional genomic-receptor actions of the hormone.\textsuperscript{58} Most recently, Leonelli et al\textsuperscript{59} have shown that long-term treatment with progesterone can reduce experimentally induced diabetic neuropathy in rats, a finding consistent with the hormone’s reported effects on myelin production. In summary, 65 animal studies conducted by 20 research groups working with 4 species (rats, cats,\textsuperscript{60} mice,\textsuperscript{61} and rabbits\textsuperscript{62}) have reported that progesterone exerts neuroprotective effects.

**Negative Preclinical Studies**

A few studies have failed to demonstrate positive effects of progesterone treatment.\textsuperscript{37,63,64} Azcoitia et al\textsuperscript{65} reported that progesterone was not protective to rats given a chemical injury with kainic acid. Murphy et al\textsuperscript{63} investigated whether 3 weeks of pretreatment with progesterone, followed by cessation of treatment at injury, improves outcomes after permanent middle cerebral artery occlusion in rats. Not only was pretreatment ineffective but also it appeared to exacerbate striatal stroke injury. Unlike other studies, which administered treatment shortly after injury, Murphy’s group pretreated their animals for 3 weeks with high-dose progesterone (30 mg/kg) and then abruptly stopped treatment at injury. Rather than weakening the case for progesterone, their findings support the notion of a “withdrawal effect,” first reported by Cutler et al.\textsuperscript{62}

**ESTROGEN**

If progesterone is helpful in the setting of brain injury, might estrogens be helpful as well?\textsuperscript{66,67} There is some evidence that estrogen, like progesterone, exerts beneficial effects on recovery in animal models of traumatic brain injury and stroke.\textsuperscript{68} Animal studies suggest that estrogen may limit secondary brain damage such as apoptosis (see below) during the acute and more chronic stages of injury. However, recent studies have failed to obtain any beneficial effects in a permanent stroke model.\textsuperscript{69}

The current literature on stroke suggests that before menopause, female victims recover from brain damage more quickly than male victims and have fewer cognitive impairments.\textsuperscript{70} These findings appear to be borne out both by epidemiologic studies and by animal research. Nakamura et al\textsuperscript{71} looked at the effects of both endogenous and exogenous estrogen levels on the outcome of intracerebral hemorrhage in rats. They found that females had far less edema than males. The team also noted that injections of estradiol in males (but not females) dramatically reduced levels of edema.\textsuperscript{71} Won et al\textsuperscript{72} also found evidence that estradiol is neuroprotective after middle cerebral artery occlusion in female rats.

Merchenthaler et al\textsuperscript{73} showed that the estrogen receptor is directly implicated in neuroprotection of the hippocampus. This group\textsuperscript{74} used focal ischemia in mice and gerbils to show that estrogen pellets implanted before or immediately after the stroke injuries prevented the selective apoptotic loss of neurons in the dorsal hippocampus, which is very susceptible to ischemic injury. Other investigators\textsuperscript{75} showed that pretreatment with either estrogen or progesterone could prevent excitotoxic and oxidative stress injury, enhancing cell survival in cultures of embryonic hippocampal neurons.

Researchers have reported that older animals with permanent ischemic stroke appear to benefit from pretreatment with estradiol. Wise et al\textsuperscript{66} subjected 3- to 4- and 9- to 12-month-old female rats to middle cerebral artery occlusion after about a week of treatment administered in Silastic capsules implanted under the skin. They found very significant estradiol-induced decreases in the sizes of the infarct volumes in both the young and middle-aged groups even when relatively low doses of estrogen were used.\textsuperscript{66}

Would estrogen therapy produce similar benefits in males? Toung et al\textsuperscript{76} created infarcts by carotid occlusion in male rats given 17\textbeta-estradiol implants or single injections before injury. Acute and chronic treatments significantly reduced the size of the infarct and were equally effective. These results are consistent with other work\textsuperscript{38,75,77} showing that estrogen treatment might enhance morphologic and cognitive recovery in brain-damaged males.

Despite signs of benefit in certain injury models, others have reported that estrogen worsens neuropathology. In a model of transient focal ischemia caused by 4-vessel occlusion, Harakuni et al\textsuperscript{78} found that loss of hippocampal pyramidal cells was substantially reduced in ovariectomized animals (32% loss) compared to their counterparts with intact ovaries (up to 54% loss). In addition, higher levels of estradiol in the serum were correlated with greater hippocampal cell loss.

**MECHANISMS OF ACTION**

Unlike treatments that target a single mechanism, such as N-methyl-D-aspartate receptor blockers, progesterone appears to act on multiple levels and pathways to interrupt or slow destructive processes. Although other pluripotent drugs, such as corticosteroids and barbiturates, have not proven beneficial, their targets of action are less clear and probably differ from those of progesterone. In contrast, progesterone limits the development of cerebral edema through several specific modes of action; for example, up-regulating the inhibitory neurotransmitter GABAa, decreasing lipid peroxidation and oxidative stress, limiting the release of inflammatory cytokines, and decreasing cellular apoptosis.

**Reduction of Cerebral Edema**

Several laboratory studies have demonstrated that uncontrollable cerebral edema accounts for much of the morbidity and mortality associated with traumatic brain injury. Inflammatory reactions initiated by brain injury, stroke, brain tumors, and other insults trigger the breakdown of brain tissue,
which leads to the development of cytotoxic cerebral edema and cell loss. Disruption of the blood-brain barrier produces vasogenic edema, allowing plasma fluid to enter the brain parenchyma. The resultant swelling increases intracranial pressure, compromising cerebral perfusion and worsening neuronal loss. Blood-brain barrier integrity is compromised in many models of neuroinjury.

In laboratory animals, progesterone reduces cerebral edema through a number of mechanisms. First, it stabilizes the blood-brain barrier, thereby preventing the indiscriminate flow of ions, water, and other inflammatory molecules across the membrane. Second, it modulates aquaporins (specifically aquaporins 4 and 9), molecules that act as osmosensors and control water drainage into the ventricles of the brain. This regulates swelling and ion exchange. Third, progesterone reduces the second (cytotoxic) phase of edema caused by the accumulation of fluid inside neurons and reactive astrocytes. This form of edema can disrupt cells and cause the release of additional toxic agents into the brain parenchyma, producing an ongoing cycle of secondary cell death.

Up-regulation of GABA

Several research teams have reported that progesterone up-regulates GABAa, an inhibitory neurotransmitter in the central nervous system. GABA-mediated inhibition can decrease excessive injury-induced excitotoxicity caused by the release of glutamate or other excitatory neurotransmitters.

Antioxidant Effects

Progesterone does not have the characteristic chemical structure of an antioxidant, but high levels of the hormone appear to reduce free radical damage. Pregnancy can reduce lipid peroxidation in brain homogenates and mitochondria. Progesterone administration reduces lipid peroxidation in different types of in vitro free-radical-generating systems in a dose-dependent manner. Collectively, these studies suggest that progesterone reduces lipid peroxidation and oxidative stress, most likely by decreasing the generation of free radicals and enhancing endogenous free radical scavenging systems.

Reduction of Inflammatory Cytokines

Progesterone and its active metabolites are also potent antagonists of central nervous system inflammation after traumatic brain injury. Two key mechanisms, both triggered by traumatic brain injury and stroke, appear to play a role: antagonism of cytokine release and inhibition of immune cell activation and migration. Contusion injuries produce a marked inflammatory reaction, with heavy gliosis seen in brain areas proximal and distal to the injury. Cytokines are potent activators of the inflammatory process. Progesterone acts at the earliest point in the cytokine cascade by modulating gene-response elements (D.G. Stein, unpublished data). Perhaps the most important mechanism underlying progesterone’s protective properties is prevention or slowing of inflammatory reactions induced by cytokines (interleukin-1, interleukin-6, tumor necrosis factor, and others).

Decreased Apoptosis

Last, progesterone appears to reduce neuronal apoptosis. At the genomic level, nuclear factorκB (NFκB) has recently been implicated in the initiation of neuron inflammation and apoptosis after traumatic brain injury. At the transcriptional level, progesterone reduces both the nuclear concentration of NFκB and expression of NFκB target genes. After progesterone treatment, mitochondrial RNA and protein for NFκB-regulated inflammatory factors such as interleukin-1β, C3, inducible nitric oxide synthase, and cyclooxygenase-2 are significantly reduced.

EPIDEMIOLOGIC RESEARCH

Several epidemiologic studies have investigated whether sex is associated with better or worse outcomes after traumatic brain injury. A positive association between recovery and female sex would provide indirect evidence that hormonal status influences outcome in traumatic brain injury. The results to date are inconclusive. A meta-analysis performed by Farace and Alves pooled data from 8 early studies of this question. They found no evidence of sex-related effects. But it is difficult to reach a firm conclusion from this analysis because the studies used widely different outcome measures. More recent epidemiologic studies have failed to clarify matters. Grosswasser et al reported that female patients achieve better functional outcomes as measured by return to school or work. They postulated that the differences are due to the effects of progesterone. Conversely, Farin and Marshall reported worse brain edema and a trend toward poorer Glasgow Coma Scale outcome scores among female patients younger than 50 years. Many of the female patients in this study experienced hypotension, an event known to independently worsen outcome. Kirkness et al reported poorer Glasgow Coma Scale Outcome–Extended and Functional Status Examination scores among brain-injured women older than 30 years compared with similarly injured men.

None of these epidemiologic studies were able to determine hormonal status at injury, whether by measuring serum progesterone levels, ascertaining subjects’ use of birth control pills, or determining subjects’ menstrual status at injury. Few of the studies adjusted adequately for sex-specific differences in injury mechanism or severity or corrected for the confounding effects of hypoxia, hypotension, or extracranial trauma. Even if every potentially confounding factor could be carefully measured and taken into account, levels of progesterone normally present in the bloodstream of nonpregnant women may be inadequate to provide significant neuroprotection in humans. It might be possible to study whether pregnant women, who have higher circulating levels of progesterone,
recover better than men after a traumatic brain injury. To the best of our knowledge, such a study has not been done.

The findings of the prematurely terminated Women’s Health Initiative study further cloud the risk-benefit picture for the use of sex hormones as neuroprotectants. The Women’s Health Initiative found that long-term treatment with low doses of estrogen and Provera (medroxyprogesterone acetate [MPA], a synthetic “progesterone-like” molecule) increases a woman’s risk of heart disease and stroke. Before extrapolation of these findings to use of progesterone for neuroprotection, there are critical issues to note. First, the Women’s Health Initiative study administered MPA with estrogen, a known procoagulant.99 Second, participants in the Women’s Health Initiative study took both hormones for prolonged periods: months to years. This sharply contrasts with use of progesterone as a neuroprotectant, which generally involves administering a high dose of natural progesterone for relatively brief periods (ie, 1 to 7 days). Third, MPA exhibits different molecular and clinical properties from natural progesterone.100 This is an important point; synthetic progestins in general have different clinical properties and may not all be neuroprotective. This is the case for MPA, a progestin widely available on the market. Stein’s team found that although MPA reduces cerebral edema after traumatic brain injury, it does not improve functional outcome.100 Other studies suggest that MPA acts differently in the brain than natural progesterone. Nilsen and Brinton101 and Nilsen et al102 found that in hippocampal neuron cultures, estrogen and progesterone, alone or in combination, protected cells from excessive glutamate-induced calcium influx toxicity. Administration of MPA not only failed to produce beneficial effects but also blocked estrogen-induced neuroprotection and enhanced calcium toxicity. MPA also blocked the expression of neurotrophic genes such as Bcl-2, whereas natural progesterone enhanced Bcl-2 and neuroprotection.

THE FIRST HUMAN TRIAL

To date, only 1 human study has evaluated progesterone as a treatment for acute traumatic brain injury. This pilot, single-site, double-blinded trial randomly allocated 100 adult patients with moderate to severe acute traumatic brain injury to receive continuous infusion of intravenous progesterone or the Intralipid carrier alone (placebo) for 3 days. The results showed that intravenous administration achieves predictable steady-state serum concentrations that do not appreciably differ by sex or injury severity.103 The study also produced preliminary evidence that the drug is safe, even in the setting of polytrauma.104 Although this pilot study lacked sufficient power to assess definitively the efficacy of progesterone treatment, promising signs of activity were observed: a marginally significant decrease in 30-day mortality among progesterone-treated patients who sustained a severe traumatic brain injury and improved 30-day functional outcomes among progesterone-treated patients with a moderate traumatic brain injury. A larger, multisite study will be needed to confirm these findings.

CONCLUSION

A large body of preclinical studies suggests that progesterone has neuroprotective properties. Progesterone has been found to be beneficial in 4 animal species and several models of neuroinjury, including blunt trauma, fluid percussion, cortical aspiration, spinal cord injury, stroke, global ischemia, and peripheral injury.

Progesterone’s most beneficial effect appears to be reducing cerebral edema, thereby limiting the increased intracranial pressure that leads to secondary loss of vulnerable nerve cells. However, there is evidence that progesterone also exerts anti-inflammatory, antiapoptotic, and perhaps antioxidant effects. These actions may work synergistically to prevent the death of neurons and glia, leading to improved functional outcomes.

Because progesterone exerts a wide range of beneficial effects, it holds promise as a treatment for several forms of acute brain injury, including blunt traumatic brain injury, penetrating brain injury, stroke, spinal cord injury, and perhaps other neurologic disorders.

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REFERENCES

2. Baulieu EE. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res. 1997;52:1-32.
7. Djebaili M, Guo Q, Pettus EH, et al. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis,


56. Cervantes M, Gonzalez-Vidal MD, Ruelas R, et al. Progesterone changes the distribution of glutamate receptor subunits in the hypothalamus of the female rat during the afternoon of the proestrous luteinizing hormone


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