CME Gender and the Injured Brain

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Anesthesiologists are frequently confronted with patients who are at risk for neurological complications due to perioperative stroke or prior traumatic brain injury. In this review, we address the growing and fascinating body of data that suggests gender and sex steroids influence the pathophysiology of injury and outcome for these patients. Cerebral ischemia, traumatic brain injury, and epilepsy are reviewed in the context of potential sex differences in mechanisms and outcomes of brain injury and the role of estrogen, progesterone, and androgens in shaping these processes. Lastly, implications for current and future perioperative and intensive care are identified.

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Anesthesiologists are frequently confronted with patients who are at risk for neurological complications due to perioperative stroke or prior traumatic brain injury. In this review, we address the growing and fascinating body of data suggesting that gender and sex steroids influence the outcome and optimal treatment plan for these patients. Clinical evaluations of neuroinjury and recovery mechanisms have resulted in many of our current concepts of neuroprotection. These concepts, however, must reflect new evidence for complex sex-linked patterns in the epidemiology, risk, and response to stroke, traumatic brain injury, and epilepsy in women versus men. In fact, tantalizing laboratory findings suggest that male and female cells simply do not respond identically to death or survival signals after injury. Furthermore, the presence or loss of hormonal steroids, i.e., the estrogens, progestins, and androgens, suppress or amplify innate gender-based differences in physiology and pathobiology. The purpose of this article is to: 1) review gender differences in mechanisms and outcomes of brain injury, 2) present evidence for the influence of sex steroids in these sex-specific responses, and 3) delineate implications for current and future perioperative and intensive care.

ISCHEMIC BRAIN INJURY

Sex Matters in Ischemic Stroke

Male sex is an acknowledged risk factor for stroke; and, in most international studies, ischemic stroke occurs more often in men than women. This sexually dimorphic epidemiology appears to be present until late in life, well beyond the menopausal years. When female and male animals are evaluated side-by-side, a male phenotype of "ischemic sensitivity" can be uncovered. In a remarkable study of more than 2000 genetically hypertensive and stroke-prone rodents, life expectancy was longer in the female than in the male. In addition, evidence of cerebral hemorrhage and vascular lesions was absent in females until an advanced age.[1] These early observations mimic human epidemiology. Furthermore, outcome from ischemic brain injury (IBI) is clearly sex-linked in genetically nonspecific animal models. Female rats and mice of many different inbred and outbred strains sustain smaller tissue damage and enjoy improved functional outcome compared with their male counterparts after an equivalent insult from focal or global cerebral ischemia.

Similar sex-specificity can be modeled in cell cultures grown without background sex steroids. Male neurons, for example, are more susceptible than female cells to challenges from pharmacological insults used to simulate brain injury, e.g., glutamate or peroxynitrite.[2] This differential sensitivity may be related to a relative inability of male cells to maintain intracellular glutathione levels after nitrosative stress. In contrast, response to oxidants such as hydrogen peroxide is gender neutral.[2] These observations do not appear to be limited to neurons. Cell death after oxygen-glucose deprivation is less extensive in female astrocytes[3] and in hippocampal slices from females.[4] These findings suggest that sex-specific sensitivity to cerebral ischemia is partly a function of the sex of cells. However, hormonal influences should not be discounted in our understanding of post-IBI cell death and recovery.

Estrogen and IBI: What We Know From the Bench

Today, there is a large body of evidence suggesting a protective effect of estrogen in a variety of experimental models of stroke. Studies of focal as well as global brain ischemia in various rodent models have

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consistently shown that female animals sustain less tissue damage than males after similar insults.[5–8] This beneficial effect of female gender is lost in reproductively senescent animals[7] or after ovariectomy but can be restored by estrogen supplementation.[7,9–11] Estrogen treatment proved similarly beneficial in male animals.[12–14] Although most of these animal studies emphasized infarct size and cell loss early after the insult, chronic estrogen supplementation also improved functional outcome.[15,16] The effects of chronic estrogen exposure in these models may explain some of the female advantage in IBI, and they are the focus of recent studies in primary stroke prevention. However, since long-term treatment before a perioperative brain insult is obviously not an option for neuroprotection, the efficacy of acute treatment with estrogen in the perioperative setting at or after onset of ischemia has also been tested in experimental ischemia and found to reduce brain damage.[17,18] This benefit also extends to male animals.[12]

Researchers have invested considerable time and effort to determine the mechanisms of estrogen protection. A profound understanding of these mechanisms is required to develop drugs that mirror estrogen's neuroprotection without the undesirable hormonal effects, particularly for male patients. Furthermore, understanding how a patient's hormonal profile may affect brain injury in the perioperative phase will help the clinical anesthesiologist design a more individualized anesthetic regimen. Estrogen elicits a cascade of cellular and subcellular actions that involve both genomic and non-genomic mechanisms after an ischemic insult. These actions can 1) stabilize the blood–brain barrier[19] and subsequently reduce brain edema,[20] 2) dilate vasculature[21] to increase cerebral blood flow,[6,9,22] 3) suppress inflammation,[19,23,24] and 4) upregulate cell-survival mediators.[25–27] In addition, estrogen is an antioxidant that can prevent lipid peroxidation.[28–30] *N*-methyl-D-aspartate (NMDA) receptor activation may contribute to estrogen-mediated neuroprotection,[31] but, at least in higher doses, estrogen can also directly inhibit NMDA receptors,[32] ameliorating excitotoxicity. Recently, investigators also recognized benefits provided by estrogen that extend beyond acute injury and positively influence regeneration and plasticity of new neurons after ischemia.[33] This may contribute to the improved memory function outcome after ischemia that is seen in estrogen-supplemented animals.[16]

In classical estrogen signaling, 17β-estradiol (E2), the predominant human estrogen, binds to an estrogen receptor (ER), usually ER-α or ER-β, which translocates to the nucleus and binds to an estrogen-response element (ERE) on the target gene to activate transcription. Both ER-α and ER-β are widely expressed under physiologic conditions in all cell types throughout the brain, i.e., neurons, glia, and endothelial cells, including in ischemia-sensitive areas such as neocortex and hippocampus.[34–37] Not surprisingly, concentrations of ER-α and ER-β are higher in adult females compared with males.[38] Transcriptional regulation of genes that do not carry an ERE has also been described via activation of a variety of non-ER transcription factors. In addition to classical transcriptional gene activation, E2 elicits non-transcriptional rapid signaling action, possibly through interaction with membrane-bound G-proteins. Rapid actions include modification of protein phosphorylation and levels of intracellular second messengers such as cyclic adenosine monophosphate or calcium. Figure 1 and Table 1 provide information on studies that describe the main signaling pathways by which estrogen affects physiological changes to reduce IBI.

Despite solid experimental evidence that E2 is neuroprotective in stroke, some investigators have found no effect or even detrimental effects of E2 in experimental ischemia. Such findings may be related to the dose of E2 used, since neuroprotection may be lost or detrimental effects may occur at higher doses.[39,40] E2 may also be less beneficial with increased severity of injury, e.g., prolonged or permanent vessel occlusion as opposed to transient occlusion.[41,42] In some models of comorbidity, such as diabetes, E2 increases infarct size[43] and postischemic inflammation.[44,45] Some of these effects may be model-related. A recent study found that E2 replacement reduced infarct size as well as systemic and brain inflammation only if it was initiated immediately after ovariectomy, but not after a prolonged period of hypoestrogenicity.[46] The mechanisms behind this dichotomy are unclear, but may be related to an inability to upregulate the expression of ERs in response to ischemia that was seen in animals exposed to prolonged hypoestrogenicity.[46] Other effects of ovariectomy besides the removal of endogenous sex hormones, such as reactive upregulation of pituitary hormones, may also account for some of the findings in animal studies. Unfortunately, this question has not been addressed. Age may also be a confounding factor, as ERalpha expression increases in reproductively senescent females.[47] Overall, while most experimental data support a beneficial effect of E2 in IBI, the dissenting findings emphasize that E2-mediated neuroprotection may depend on the specifics of the experimental and clinical situation. More work is clearly needed to define the circumstances under which E2 can be expected to show its full neuroprotective potential.

Progesterone and IBI: What We Know From the Bench

Fewer studies have focused on the effects of progesterone, the "other" female hormone, on IBI. Most reports identify beneficial effects of progesterone and its metabolite, allopregnanolone, in a variety of experimental injury models, including focal and global cerebral ischemia. Both cell survival, assessed as lesion volume,[48–52] or neuronal density,[53–55] as well as functional neurologic outcome[49,50,56] are improved by acute or chronic progesterone treatment in male[56] and

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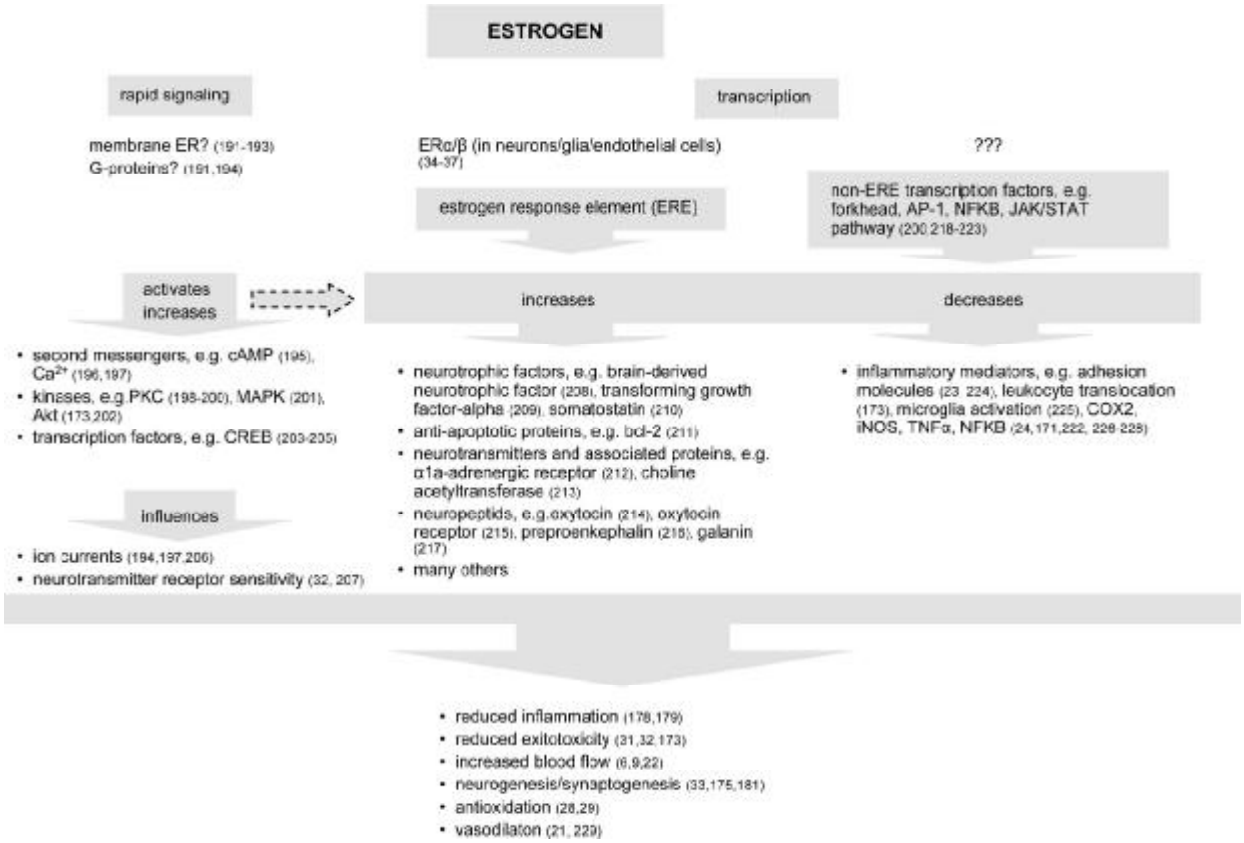

Figure 1. Relevant estrogen signaling pathways in ischemic brain injury.

Table 1. Summary of Potential Estrogenic Mechanisms of Neuroprotection in Ischemic Brain Injury

Proposed mechanism	Reference
Preservation of intraischemic blood flow	7
Improvement of postischemic reperfusion	18
Stabilization of blood–brain barrier	171
Reduction of cerebral edema	20
Antioxidant activity	28,172
Amelioration of excitotoxicity	32,173
Up-regulation of cell-survival mediators	25,26,174
Increase of neurite outgrowth and spine density	175,176
Increase of neurotrophic factors	177
Reduction of leukocyte adhesion after transient global ischemia	178
Suppression of microglial activation	179
Reduction of reactive gliosis	180
Increase of neuronal stem cell proliferation	33,181

female[7] animals. However, Murphy et al. reported that chronic progesterone treatment is associated with exacerbated striatal injury after focal ischemia in ovariectomized rats.[57]

After brain injury and ischemia, progesterone stimulates protective pathways that suppress inflammatory response,[58–60] i.e., reduce expression of proinflammatory cytokines and decrease post-stroke edema[58]; but the exact molecular mechanisms involved remain unclear. We know that progesterone, but not allopregnanolone, binds to the progesterone receptor, sigma receptors, and the putative membrane progesterone binding site,[61,62] which may be important steps in the neuroprotective pathways. Finally, both allopregnanolone and progesterone activate γ-aminobutyric acid-A ($GABA_A$) receptors, protecting neurons from *in vitro* ischemia.[63]

Female Sex Steroids in IBI: Clinical Trials and Implications for the Anesthesiologist and Intensivist

Despite the abundant epidemiologic and experimental data that support the beneficial effects of female sex hormones in brain injury, and specifically cerebral ischemia, no clinical studies have substantiated any benefit of estrogen or progesterone treatment in the context of stroke. Neither have estrogen nor progesterone been studied clinically as an acute treatment for perioperative brain injury, although experimental data suggest that they may reduce injury and improve outcome. Since side effects of an acute, likely single-dose, treatment regimen are expected to be limited in both men and women, clinical trials appear to be warranted.

Much of the recent interest in clinical trials has focused on long-term, chronic female hormone treatment, i.e., hormone replacement therapy (HRT). Large studies, including the National Institute of Health-sponsored Women's Health Initiative, have linked HRT to increased risk for incidental stroke. The Women's Health Initiative studied two parallel groups: women

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after hysterectomy were randomized to receive either conjugated equine estrogen or placebo, and women with an intact uterus were randomized to receive combined estrogen and progestin or placebo.[64] Quite unexpectedly, in light of the epidemiologic data supporting a reduced incidence of stroke in premenopausal women, initial results from the Women's Health Initiative showed an increased risk for first-time stroke in both groups of otherwise healthy postmenopausal women[65]; and the study was terminated prematurely. E2's hormonally inactive optical isomer, 17α-estradiol, was tested in a phase I clinical study and was determined to be safe for human use.[66] However, data supporting an actual neuroprotective effect in humans are currently lacking.

Are there any clinical implications, then, for the anesthesiologist and intensivist? Despite the overwhelming experimental evidence for the neuroprotective effects of female sex steroids in IBI, there is an alarming paucity of clinical data. Consequently, there are currently no recommendations for the use of acute estrogen or progesterone treatment to afford protection in perioperative brain injury. Furthermore, no clinical studies have attempted to define gender differences in anesthetic neuroprotection. Although years of laboratory research have convinced most anesthesia providers that commonly used anesthetic drugs are more or less potent neuroprotectants,[67,68] all of the relevant research was performed exclusively in males. It is unclear at this time if females enjoy the same level of protection by anesthetics. Recent work on anesthetic preconditioning has shown, however, that isoflurane does not induce tolerance to experimental stroke in gonadally intact female rodents as it does in intact males; and, in fact, females sustain greater damage.[68] Neuroprotection by the anesthetic drugs isoflurane and xenon involves activation of Akt[69] or CREB,[70] neuroprotective mediators that can also be activated by E2. Surprisingly, however, Kitano et al. also found that while isoflurane preconditioning induced Akt activation in brains of male mice, this was not the case in females.[68] In the context of anesthetic preconditioning, E2 therefore may prevent rather than induce the activation of neuroprotective pathways. More definitive studies on this phenomenon are urgently needed to ensure optimal safety when developing an anesthesia plan and choosing the anesthetic drug, particularly, for female patients at risk for perioperative stroke.

In light of the adverse findings of the recent HRT trials and the complete lack of clinical studies on the effects of gender and sex hormones on perioperative IBI, many questions that are crucial to the routine and safe practice of anesthesiology and critical care have to remain unanswered at this time. Should anesthesia providers concerned about perioperative ischemia be more inquisitive about the hormone status of their female patients? Should we possibly try to manipulate this status to include recommendations at preanesthesia visits to continue or stop HRT and contraceptives? Clinical evidence for the effects of endogenous hormones on perioperative IBI is abysmal; and there are no relevant clinical trials. Experimentally, infarct size after focal ischemia is inversely related to the levels of circulating estrogen in normal cycling female rats.[71] Although this suggests that elective high-risk surgery may be "safer" for the brain on days when endogenous estrogen levels are high, is this sufficient evidence to recommend scheduling such surgery according to the menstrual cycle of the premenopausal patient? Until we have more clinical data, most providers will likely answer this question in the negative, but more work is clearly needed to develop clinical evidence. Some have suggested discontinuing HRT and contraceptives prior to elective surgery to reduce the risk of perioperative thrombosis.[72] Will this practice, however, put the brain at higher risk in the case of perioperative ischemia? Should recommendations be based on the perceived risk of the planned surgery? If so, what data would we use to establish the relative risk of perioperative thrombosis versus stroke? Similarly, should HRT be continued in the intensive care unit (ICU) after stroke or traumatic brain injury (TBI)? Although outpatient cardiac medications will almost certainly be continued, hormones are more likely to be discontinued, since they tend to be viewed as unimportant or even dangerous due to their thrombogenic potential. What are the effects of acute hormone withdrawal on brain injury and outcome? Considering that E2 suppresses inflammation after brain injury, should optimal levels be maintained in these critically injured patients, and what are optimal levels? All of these questions are admittedly pointed and provocative, and they are far from being answered definitively. Nevertheless, they may help to emphasize the gap between experimental data and clinical trials that needs to be narrowed before clinical practice can change. Hopefully, they will also raise awareness among anesthesia providers of the relevance that gender and sex hormones may have in the perioperative period.

TRAUMATIC BRAIN INJURY

Sex Differences and Neuroendocrine Abnormalities

TBI is a major cause of death and disability worldwide and is the leading cause of death between the ages of 15 and 44 yrs. Head injuries account for the majority of all trauma-related deaths; and at least 6.2 million people in Europe and 5.3 million in the United States live with disability, impairment, or handicap from TBI.[73]

Young adult males are at highest risk for TBI, but the male/female incidence ratio reaches 1:1 at age 65 yrs.[74] The strong relationship between age and TBI outcome has been demonstrated in numerous prognostic studies. Results from an IMPACT (International

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Mission on Prognosis and Analysis of Clinical Trials) study of TBI confirm the previously described direct association between age and volume of the lesion, particularly in acute subdural hematomas.[74] This observation has direct consequences for health care planning due to increasing age of the population and increasing incidence of TBI in the elderly.[74–76]

Reports on gender-related differences in outcome after TBI have raised interest in hormonal influences and generated research into neuroprotective effects of estrogen, progesterone, and testosterone. Women were sometimes excluded from early studies due to concerns regarding effects on fecundity and the influence of hormonal fluctuation on drug pharmacokinetics. More recent studies indicate poorer TBI outcome in females,[77–81] whereas only a few investigators report a better outcome.[82] In a prospective study of severely and moderately brain-injured individuals, Kraus et al. found that females were 1.75 times more likely to die of their brain injury than males and were 1.57 times more likely to experience poor outcomes, i.e., severe disability or persistent vegetative state.[83] Mushkudiani et al. used data from an IMPACT study to describe and quantify the prognostic value of demographic characteristics, including gender, on six-month TBI outcomes assessed by the Glasgow Outcome Scale.[74] They extracted individual patient data based on age ($n = 8719$), gender ($n = 8720$), race ($n = 5320$), and education ($n = 2201$) from eight therapeutic phase III randomized clinical trials and three surveys involving moderate or severe TBI. Analysis demonstrated a reciprocal relationship between outcome and increasing age, but no correlation between gender and outcome was found in this study. The investigators concluded, therefore, that outcome after TBI is dependent on age, race, and, to a lesser extent, on education, but not on gender.

Despite a lack of consistent clinical data regarding gender differences in TBI, a growing body of evidence from laboratory and clinical research supports the influential role of sex hormones in injured brain. Several studies have also focused on gender-specific changes associated with TBI. Reproductive function, for example, is downregulated in episodes of severe illness, including TBI.[84,85] Hypopituitarism often occurs in the post-acute phase of TBI and may normalize later; however, it may also develop after the post-acute phase. Schneider et al., described the prevalence of anterior pituitary insufficiency at 3 mo (56% of all patients) and 12 mo (36% of all patients) after TBI. At 3 mo, the extent of hypogonadism was directly proportional to the severity of disease.[86] At 12 mo, however, the clinical improvement noted was significantly less marked in male patients, due possibly to low testosterone levels or greater severity of disease. In fact, a decline in testosterone that is dependent on the severity of the injury and is also reversible has been reported in studies of the early phase after TBI.[87,88] Agha et al. evaluated the prevalence of anterior and posterior pituitary dysfunction in the early phase after TBI.[89] Eighty percent of patients had gonadotropin deficiency. In males, there was a direct correlation between serum testosterone concentration and Glasgow Coma Scale assessment. Similarly, Dimopoulou et al. found that 53% of their TBI patients had an abnormal result in at least one hormonal axis tested during the early recovery period, and cortisol hyporesponsiveness and gonadal dysfunction were equally common in males and females.[90] Interestingly, these endocrine abnormalities were associated with a higher brain computed tomography scan classification score.

In summary, we recommend that neuroendocrine abnormalities be assessed more carefully after TBI since they may have significant implications for recovery and rehabilitation. To confirm that sex steroids mediate gender differences in TBI outcome, more clinical studies are needed; however, there is already sufficient evidence to warrant considering restoration of gonadotropin levels in practice. For example, male TBI patients in the ICU or the operating room could benefit not only from restoring their testosterone levels, especially in the early phase, but also from monitoring these levels long-term for at least 3 mo or even 12 mo. Other studies suggest that progesterone treatment may improve outcomes for men and women.

Progesterone and TBI: What We Know From the Bench

The influence of sex steroids in trauma-induced brain damage was first considered with the observation that females develop less edema[91] and sustain reduced cortical contusions compared with males.[92] Focus then centered around progesterone because edema is virtually absent in states of hyperprogesteronemia in females.[91,93] Progesterone is present in small but approximately equal concentrations in male and female brain, and progesterone receptors are widely distributed throughout the central nervous system.[94]

Research studies in animal models of TBI confirm the neuroprotective effects of progesterone (Table 2). Progesterone is beneficial in ischemic as well as traumatic brain injury (Fig. 2). In fact, at comparable doses, progesterone yields effects that are reproducible across species and types of brain injury. In 2003, Goss et al. published a dose-response study demonstrating that 8–16 mg progesterone/kg body weight is optimal to promote cognitive recovery after TBI.[95] More recently, Sayeed et al. found that allopregnanolone is even more effective in facilitating central nervous system repair.[52]

Method of delivery also affects the efficacy of progesterone. The pharmacokinetics of progesterone indicates that the half-life of this neurosteroid in serum is approximately 15 min, and it is fully metabolized by 24 h.[96–98] This results in a spiking effect that is attenuated by subcutaneous delivery, as the bolus of

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Table 2. Neuroprotective Effects of Progesterone in Traumatic Brain Injury (TBI): A Summary of Laboratory Findings

Species/gender/model	Proposed mechanism	Reference
Rat/male (M), female (F)/TBI	Reconstitutes blood–brain barrier, reduces brain swelling in M,F	182
Rat/M,F/TBI	Reduces vasogenic and cytotoxic edema in M,F	182
Rat/M,F/TBI	Reduces edema when treatment is delayed 24 hr in M,F	117
Rat/M,F/TBI	Reduces brain water content in M,F	91,182,183
Rat/M,F/TBI	Improves motor performance in F	183
Rat/M/TBI	Reduces lipid peroxidation	184
Rat/hippocampal neurons	Reduces free radical formation	185
Rat/F/brain homogenate	Reduces lipid peroxidation	186
Rat/primary cortical neurons = Hippocampal HT22 cells human brain homogenates	Reduces lipid peroxidation	29
Human/M,F/TBI	Decreases isoprostane levels in F	80
Rat/M/TBI (prefrontal injury)	Reduces proapoptotic, increases antiapoptotic enzymes	187
Rat/M/TBI	Reduces expression of proinflammatory genes	188
Rat/F/TBI	Protects thermoregulation	189
Rat/M/TBI	Enhances functional recovery	95
Mice/M,F/TBI	Improved performance in M	190
Rat/M,F/T	Improved motor performance in F	183
Rat/F/progesterone withdrawal	Increased anxiety	108

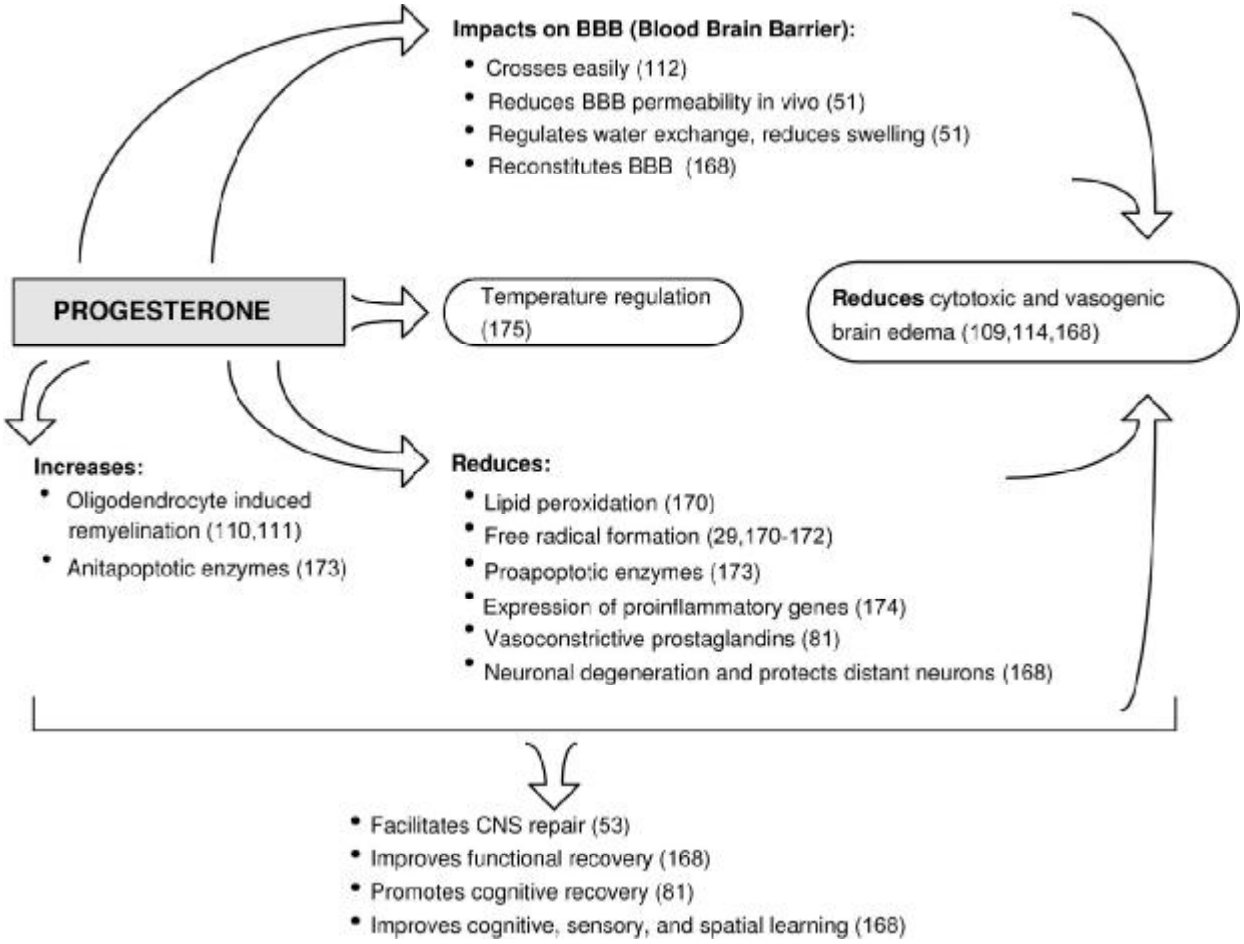

Figure 2. Progesterone effects in ischemic and traumatic brain injury.

drug seeps into tissues at a slower rate.[99–101] Cutler et al. demonstrated that, in a rat model of TBI, continuous progesterone release treatment is more beneficial than daily subcutaneous bolus injections over the same period of time.[102] Treatment is optimized by delivering a continuous infusion of progesterone over 5 days, and the adverse effects of acute progesterone withdrawal are reduced with gradual tapering by 1 week postinjury. In contrast to tapered withdrawal, acute progesterone withdrawal is characterized by increased apoptosis, inflammation, and anxiety behaviors during the acute recovery phase after TBI.

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acute progesterone withdrawal occurs when the linkage between allopregnanolone and receptors that activate GABA is suddenly terminated, causing an upregulation of NMDA and sigma receptor binding, which, in turn, leads to increased anxiety, depression, and seizure susceptibility.[103–108] Furthermore, continuous progesterone infusion provides a model better suited to inform clinical trials for progesterone use after TBI.

In summary, laboratory results indicate that, in males and females, progesterone treatment after TBI dramatically reduces edema[109] and subsequent neuronal degeneration,[110,111] restores the integrity of the blood–brain barrier,[112] and improves spatial learning performance. Clinical findings substantiate benefits of progesterone treatment.

Progesterone and TBI: Clinical Trials and Implications for the Anesthesiologist and Intensivist

Progesterone is an attractive candidate for the treatment of TBI because it is lipid soluble and can, therefore, rapidly cross the blood–brain barrier, reaching equilibrium with plasma within an hour of administration.[113] It also has a long history of safe use in men and women.[114] Although the neuroprotective potency of progesterone has been successfully studied in the laboratory, it is extremely difficult to translate its efficacy into clinical benefits.[73] Outcome after TBI depends not only on the nature and severity of the injury and the subsequent treatment, but also on the unique, constituent characteristics of each individual patient. For example, Farin et al. studied males and females with severe head injury and described greater susceptibility to brain swelling in females 50-yrs-of-age and younger, with a possible benefit from more aggressive monitoring and treatment of intracranial hypertension in this group.[115] They postulated that higher levels of estrogen relative to progesterone in these patients may be responsible for this sensitivity.

In 2005, Wright et al. reported that IV progesterone could be administered in effective doses via a peripheral line to adult victims of acute TBI.[116] Their formulation, which is now widely available in inexpensive, generic forms, was used in ProTECT, a clinical trial to assess the safety and potential benefit of administering progesterone to patients with acute TBI. In 2007, Wright et al. reported the results of this phase II, randomized, double-blind, placebo-controlled trial, conducted at an urban Level I trauma center.[94] One hundred adult trauma patients who arrived within 11 h of injury with a post-resuscitation Glasgow Coma Scale score of 4 to 12 were enrolled in this trial with proxy consent. Seventy-seven patients received progesterone, and 23 received placebo. The groups had similar demographic, clinical, and laboratory characteristics. Results showed that the 30-day mortality rate in the progesterone group was lower than in the control group. Furthermore, survivors of moderate TBI who received progesterone were more likely to have a moderate to good outcome than those randomized to placebo. Although no significant differences were observed between treatment and control patients in mean intracranial pressure or in the relationship of intracranial pressure to therapeutic intensity levels, this study lacked sufficient power to assess the effects of progesterone on intracranial pressure.[94]

The Wright et al. study concluded that progesterone caused no discernible harm and may be a beneficial treatment for TBI. The investigators speculated, however, that proxy consent delayed initiation of treatment by several hours. One study of TBI in an animal model suggests that progesterone may yield favorable effects as late as 24 h postinjury, but the benefit is greatest if treatment is administered within 2 h.[117] Early initiation of treatment, perhaps through exception to informed consent, would maximize potential therapeutic benefits and should be considered for future clinical trials of this agent.[94] A larger trial involving multiple clinical sites, randomization 1:1, and rapid initiation of treatment is still warranted.

In summary, noninvasive progesterone treatment is potentially beneficial for improving functional and cognitive recovery in TBI patients. It may also help to prevent and treat intracranial hypertension, although drug interactions with mannitol and other therapeutics must be addressed. Progesterone, unlike estrogen, can be administered to both genders without significant side effects. Ease of delivery and a relatively large window of opportunity also make progesterone very attractive. Although the clinical data may not be complete, anesthesiologists and intensivists can still consider using this neurosteroid in the ICU and the operating room, especially in the early phase of TBI. Special attention should be paid to women receiving contraceptives and HRT. If HRT is discontinued, the sudden decrease in progesterone and/or estrogen levels may negatively impact TBI outcome and can even cause acute withdrawal; therefore, continuation of hormonal treatment in the ICU and operating room may be beneficial and may also prevent withdrawal symptoms. Furthermore, TBI in pregnancy remains largely unexplored, but hyperprogesteronemia reduces brain edema.[91,93]

Epilepsy and Gender

Many epidemiologic studies suggest sex differences in the incidence of epilepsy. These differences appear to be closely linked to the type of seizure disorder. Overall epilepsy incidence may be higher in males,[118,119] but women are more likely to suffer from idiopathic generalized epilepsy[120,121] or absence seizures.[118] Because the menstrual cycle influences the occurrence of complex partial seizures involving the limbic system[122–127] and menopause largely eclipses gender differences in epilepsy incidence, sex steroids appear to play a significant role in these underlying disease processes.[128] In fact, increased seizure incidence is associated with low estrogen and low progesterone

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phases and with the follicular phase when plasma estradiol sharply increases; however, seizure activity decreases when progesterone is high relative to estrogen.[93] Experimental studies in animal models confirm these clinical findings.[129–135]

Such observations form the basis for hormone treatment of epilepsy. Progesterone is used to treat women with catamenial epilepsy.[122–124,126,131,136–138] Progesterone treatment also reduces limbic seizures in a variety of experimental models;[129,139,140] however, its beneficial effects are observed only at low physiological levels.[141] Progesterone's anti-epileptic mechanisms likely involve $GABA_A$ receptor modulation.[142–145] In contrast, estrogen can increase seizure potential in animals, but it may also provide some protection against neuronal injury from seizure.[146,147] These neuroprotective effects are dependent on a number of variables, including 1) treatment duration, 2) latency before seizure testing, 3) mode of administration, 4) estrogen dose and hormonal status, 5) estrogenic species, 6) the region/neurotransmitter system involved, 7) seizure type/model used, and 8) sex.

Care should be taken, however, when prescribing hormone therapy for women with epilepsy; and the decision to continue or discontinue contraceptives, HRT, or other hormone preparations during the perioperative period should be made with special consideration in these patients. Conjugated equine estrogens, such as Premarin, for example, can be epileptogenic[148,149] and do not contain 17β-estradiol, well-documented for its neuroprotective properties (see Ischemic Brain Injury, this article). Further studies are necessary to gather the evidence required to direct prescription of hormonal preparations that may affect both seizure control and prevention of seizure-induced neuronal damage.

The Male Side of the Story: Androgens and Brain Injury

Less is known about male sex steroids and brain injury. This is due in part to poor agreement about "normal" levels of androgens in men over their lifespan. Testosterone cycles diurnally, declines progressively with age (andropause), and decreases rapidly in response to stress and illness;[150,151] however, no widely accepted normal range for serum testosterone is established for aging men, and many studies have simply applied cutoff values that are defined for young adult men.[152] Furthermore, the significance of the andropause to men's health is unclear.

Emerging data from laboratory studies suggest that testosterone and its potent metabolite, dihydrotestosterone, are important factors in the male response to cerebral ischemia and trauma. Male animals sustain larger ischemic damage compared with age-matched females for a comparable insult, suggesting a male "ischemia-sensitive" phenotype. In male rats, androgen replacement in castrates increases histological damage from stroke,[13,153,154] whereas, stressors, such as halothane anesthesia, administered before an episode of cerebral ischemia reduce testosterone levels, resulting in a 50% reduction in brain damage.[155] Furthermore, testosterone replacement after stroke accelerates functional recovery in castrated rats.[156] One interpretation of this interesting paradox is that testosterone has deleterious effects in the case of acute stroke but is beneficial during the recovery phase. Beneficial effects of androgens after peripheral nerve damage or brain trauma have also been reported in animals,[157–161] in part via interaction with glial elements.[156,160,162]

Several small-scale studies of the andropause suggest that loss of testicular and adrenal androgens has a negative impact on cognition and memory[163–165] and contributes to the well-recognized loss of muscle function and bone density. More directly relevant to perioperative complications, decreased testosterone levels have been associated with poor outcome after acute ischemic events.[166] Androgen levels are inversely associated with stroke severity, infarct size, and 6-month mortality; and total and free testosterone levels tend to normalize within 6 mo after stroke. These data do not necessarily suggest a direct causal relationship because brain injury provokes an acute stress reaction that causes a reduction in plasma testosterone. However, stress-induced acute reduction of androgens could be relevant to progression of stroke damage, e.g., by decreasing fibrinolytic activity,[167,168] which would delay lysis of a preformed thrombus. Under normal physiological conditions, androgens inhibit arterial thrombosis;[169] however, their role in vascular disease has not been well studied. Potential mechanisms by which androgens could enhance post-stroke recovery include normalization of reperfusion, promotion of axonal regeneration, synaptogenesis, and neurogenesis.[170]

Most of these observations come from anecdotal or small-scale clinical studies. Nevertheless, evaluation of the andropause with its gradual loss of male sex steroid production is gaining importance to the new area of men's health. The importance of androgens to anesthetic mechanisms or to perioperative complications remains an uncharted territory. However, new findings could have broad applications to men with brain injury from stroke or reperfusion injury after invasive neurosurgical procedures.

CONCLUSIONS

Biologic sex and sex steroids are important factors in clinical and experimental brain injury and in epilepsy. Estrogen and, to a lesser degree progesterone, have accumulated an impressive reputation as neuroprotectants in physiologically relevant doses in laboratory studies, but there are large gaps between experimental data and the application to women. Data surrounding TBI are more clear. Laboratory data strongly show that progesterone treatment after TBI reduces edema, improves outcomes and restores blood–brain barrier function. Clinical studies agree

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with these data, and there are continuing human trials for progesterone treatment after TBI. The question of why the male brain is more sensitive to some types of brain injury is an active area of research; however, androgenic effects remain largely evaluated at the bench rather than the bedside.

Despite considerable evidence emphasizing that sex differences, sex steroids and pharmacological hormones can alter outcome from brain injury, the implications for perioperative management are only beginning to be scrutinized. Although anesthetics are often thought to be neuroprotective in their own right, we know relatively little about interactions between anesthetics and sex steroids. In part, this is because preclinical studies are largely conducted in male animals. Further evidence can easily be gathered to direct the use and withdrawal of sex steroids in patients with neurovascular risk factors and seizures. Hopefully, this review will raise awareness among anesthesiologists and intensivists to the presence of clinically relevant gender differences in brain injury and to the relevance that sex hormones may have in the perioperative patient.

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