



Medical Theory: Why Does Progesterone Not Work After a Traumatic Brain Injury in Humans?

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Introduction

The evidences suggest progesterone has a neuroprotective action in preclinical studies [1], but in some recent clinical studies, this hormone did not benefit people involved in traumatic brain injury. [2,3] So, why progesterone does not work correctly after a traumatic brain injury in humans?

Traumatic Brain Injury

Traumatic brain injury (TBI) is a great public health problem. More than 50 million head injuries occur each year worldwide. [4] In 2010, a study pointed to ECT in 89% of trauma-related deaths in low and middle-income countries. And according to the same study in the spectrum of trauma-related injuries, traumatic brain injury was considered a major cause of death and disability. [5] In the United States, traumatic brain injury is serious long-term morbidity. Between 1.6 and 3.8 million sports-related injuries are reported yearly, while an estimate of 5.3 million people lives with long-term cognitive and psychological impairment. [6] The pathophysiology of traumatic brain injury is complex and involves primary and secondary mechanisms of injury. The primary lesion induces biochemical and cellular changes leading to lesions that evolve over hours, days, months or even years with definitive neuronal damage and early death. [7] These traumatic injuries are caused by direct and indirect biomechanical forces and result in an intense neurometabolic event in the brain. [8] The main process after traumatic brain injury affecting the results is acute inflammation, involving mediators such as TNF- α , IL-6, IL-8, and IL-10. [9] After brain injury, including traumatic brain injury, GFAP expression increases in astrocytes which in turn release inflammatory cytokines and disrupt functional recovery. [10,11]

Multiple lesions in trauma are commonly associated with hypotension, hypoxia, hyperpyrexia, and coagulopathy that can adversely affect the brain and have long-term consequences. In addition, a growing body of evidence indicates that traumatic brain

injury patients are susceptible to other neurological and psychiatric disorders (Table 1). In many cases, the manifestation of these associated conditions occurs several years after the injury. The disease's level of complexity limits the development of strategies and effective treatment models to predict the outcome of patients with traumatic brain injury [12-19].

Table 1: Neurological and psychiatric disorders associated with Traumatic brain injury.

Chronic traumatic encephalopathy
Dementia,
Stroke,
Parkinsonism
Epilepsy
Alzheimer's disease
Post-traumatic stress disorder

Progesterone

Some clinical studies have indicated that progesterone is a potent anti-inflammatory agent that modulates microglial activity after brain injury [20-22]. Perilesional reactive gliosis decreased broadly after progesterone administration (GFAP and Iba1 immunolabeling), with previous studies demonstrating a progesterone-induced reduction in GFAP expression after traumatic brain injury [23]. Progesterone is a pleiotropic hormone that uses multiple signaling pathways, including the regulation of gene expression after binding to intracellular progesterone receptors. In addition to the classical receptor (PR), progesterone also interacts with other signal transduction mechanisms, such as the s1 receptor (Ps1) that is a competitive inhibitor by which it can reduce N-methyl-D-aspartate (NMDA) glutamate. [24,25] Other studies have reported the attenuating effects of progesterone on edema in various animal models of brain injury. [26,27] An inverse correlation between serum progesterone level and degree

of edema has been reported. [28] A study, evaluating progesterone versus dexamethasone to reduce neurosurgical brain edema, demonstrated the safety of progesterone use and equal efficacy in cerebral edema and attenuation of acute cellular inflammatory responses. [29]. Some authors evaluated edema and brain water concentration (BWC), with progesterone analogous in guinea pigs, and reported the same result. [30, 31] Positive results from preclinical studies and phase II studies [33-35] were contradicted in phase III studies, where progesterone failed to prove its efficacy in traumatic brain injury in humans. [36, 37].

Pharmacology of Progesterone

When we evaluated the pharmacological profile of the presentations tested for clinical efficacy, most of the available drugs are poorly acidic or poorly basic and have low aqueous solubility. These poorly soluble drugs in water evolve with low absorption rates, which can result in low tissue bioavailability, being critical for their rapid and effective action, as in brain injury. [38]. The solubility dilemma is a major challenge for its formulation. [38-40] Solubility is an important parameter in obtaining drugs with the ability to achieve the desired concentration in the brain and other tissues. Due to progesterone's plasma half-life of only 25 min, it is necessary to take it to the brain rapidly, which in practical conditions would require immediate continuous IV post-trauma treatment. [41] It can be stated that the dripping or use of multiple injections in a lipid-based vehicle delays the release into the systemic circulation and results in a consequent reduction of the expected protective properties of progesterone in the acute phase of traumatic brain injury. This feature is important and makes it difficult to "replicate" the compelling results obtained in pre-clinical trials in guinea pigs. [42-44]

Conclusion

After two decades of preclinical research on the use of progesterone, it can be said that it is more than a simple reproductive hormone. [45,46] More than 100 articles on beneficial effects of progesterone have been published in four different species, including humans and 22 different models of traumatic brain injury lesions. [45-48] Although there are questions about the design and execution of clinical trials, it is important to realize that progesterone itself is not adequately soluble, thus configuring a challenge for its emergency use. [1,19,49-51] The drug solubility and the time necessary to reach concentrations in damaged brain tissue may contribute to the variability of response in patients and mask potential benefits in the injury's acute phase. We consider Hill's sentence: "All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." [52].

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