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Neuroprotective effects of progesterone in acute brain trauma and its physiological mechanism

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ABSTRACT

Traumatic brain injury (TBI) is the leading cause of death and neurological disability in young adults worldwide. This work aims to review the role of progesterone in traumatic brain injury and the usefulness as a possible treatment. We searched pubmed database (2000-2017) for articles containing "progesterone and brain traumatic injury". Basic science studies have advanced knowledge of the mechanisms of secondary brain injury, creating prospects for the medical and pharmacological management of TBI. Although several comparative studies evaluated both the efficacy and safety of several groups of drugs, in which, corticosteroids, tranexamic acid, β receptor antagonists, erythropoiesis-stimulating agents, reductase inhibitors include hydroxymethyl glutaryl-CoA inhibitors (statins), among others. Several studies even evaluated the role of progesterone in the treatment of TBI, which is providing growing evidence about its potential neuroprotective mechanisms during the acute phase of trauma. Despite recent advances in the field of management of TBI care in the emergency units, intensive care and the multiple trials for more than 20 years to find useful pharmacological treatments, most of these efforts failed in pre-clinical stages (II and III).

1. Introduction

Traumatic brain injury (TBI) is a serious public health problem in developed and developing countries; it is the first entity as a cause of mortality secondary to injury[1], which causes significant disability and healthcare related costs. While clinical treatment has greatly improved thanks to the quality of standard care provided today by health systems but failed to clearly establish effective medical treatment that improves mortality rates and reduce losses[2]. Estimates of the incidence, prevalence, severity, and consequences

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of the TBI, as well as the degree to which may be preventable, indicate that TBI causes huge individual and social losses. Therefore, efforts to boost preventive strategies are highly justified[3].

In the United States, approximately two million people suffer TBI each year and 70 000 of these die before receiving medical care; 500 000 people are hospitalized each year out of which 25 000 dies, but even worse, another 150 000 people remain with severe neurological disabled and 2 000 will continue to live in a persistent vegetative state[1,4].

In recent years, The United Stated developed an interest in TBI due in part to many injuries sustained during the explosions in Iraq and Afghanistan. Government sources indicate during 2003 to 2007, up to 43 779 survivors, injured in combat were diagnosed with varying degrees of brain injury caused by explosive devices[5]. In fact, one of the alternatives as glucocorticoids (in this case dexamethasone) even though at first was considered a gold, is now considered as harmful to the central nervous system (CNS). Another alternative was the corticosteroids, but its spread was halted when a clinical trial revealed the use of corticosteroids led to higher mortality in the trial group than the control group[6,7]. Other alternatives cyclosporin and erythropoietin which is believed to possess a neuroprotective effect in TBI[8]. The question is, why is it so difficult to find a suitable treatment for the TBI. The answer is that being an event of such magnitude, TBI constitutes a highly complex injury. Given what we know about the evolution of traumatic brain injury or stroke, there is an urgent need to find an agent that should work on multiple levels of injury, so its effect may influence on a variety of receptors that inhibit destructive cascade events after TBI, and to stimulate necessary mechanisms to improve repair and regeneration of tissues after these events have taken place.

Progesterone (P4) may be the pleiotropic drug that can significantly attenuate the cascade of complex injury associated with TBI[2,9] About more than two decades of research in the pre-clinical trial of P4 for TBI, it is clear that this complex neurosteroid has many properties affecting the mechanisms involved in neuroprotection and repair after different types of CNS injury[10].

Recently, it has been reported that P4 limits tissue damage after blunt traumatic brain injury, in stroke, spinal cord injury, diabetic neuropathy and other acute neuronal injury[11].

Studies began in 1980 with Beaulieu et al, observed usefulness of progesterone in the TBI and as the years went by, studies intensified, but the truth is that the discovery of protective effects of progesterone began with the difference in gender responses that were present before induction of the traumatic brain injury.

Although Progesterone is still widely considered primarily a sex hormone, it is an important agent affecting many functions of the central nervous system (CNS) exerting a wide range of actions depending on the target tissue, including regulating cognition status, mood, inflammation, mitochondrial function, neurogenesis and regeneration, recovery of myelination and a TBI, protection or rebuilding of the blood-brain barrier, reducing cerebral edema, downregulation of the inflammatory cascade, and reduction of neuronal apoptosis[11–13]. Research is ongoing on the effects and when using progesterone.

This work aims to review the role of progesterone in traumatic brain injury and the usefulness as a possible treatment.

2. Mechanisms of action

As has been well-studied brain's main nutrients are glucose and oxygen. The brain tissue has lower tolerance to ischemia; the brain consumes about 20% of total oxygen in the body, using only 60% to form ATP, at metabolic rate (oxygen consumption) of 3 mL to 5 mLO_2/100 g tissue/min (± 50 mL/min in adult consumption of O_2).14 A greater flow occlusion for 10 seconds, PaO_2 fell rapidly to 30 mmHg, bringing the patient to unconsciousness, and 15 seconds caused alterations in electroencephalogram (EEG), then from 3 to 8 minutes, ATP is completely depleted, initiating an irreversible neuronal injury between the next 10 and 30 minutes. Glucose consumption rate is approximately 5 mg/100g/min, with 90% aerobic metabolism[15].

Cerebral self-regulation is based on the modification of the cerebrovascular resistance (VCR, vasodilation or vasoconstriction) in order to maintain an optimal cerebral blood flow (CBF) according to O_2 brain metabolic requirements at the moment. Self-regulation is largely determined by the partial pressure of CO_2 ($PaCO_2$), by the mean arterial pressure (MAP) and to a lesser extent, PaO_2, adenosine, pH, *etc*. So when the brain $PaCO_2$ is high (greater metabolic work) the CVR falls, increasing CBF and CDO_2, and the opposite happens when the $PaCO_2$ decreases (less metabolic work). It is estimated that the CBF varies by 4% per mmHg of CO_2, in normotensive. The MAP is similar, CBF is regulated to protect the brain tissue of falls or sudden increase of pressure to endanger CDO_2, however, these self-regulations have limits, above or below which the CBF is absolutely dependent of MAP variations[15].

3. Physiopathology of TBI

The damage caused by a TBI has divided into two phases; a) Primary Injury (immediate trauma injury) and b) Secondary Slander (post-trauma metabolic cascades). The damage caused by the primary injury is impossible to reverse, however, the events of secondary injury are potentially manageable, then, the therapeutic actions should be addressed to avoid or minimize the metabolic cascades triggered by the initial injury and decrease the risks of poor neurological outcome and/or death. Immediately produced TBI, $CMRO_2$ decreases steadily, however, the CBF can vary according to maintain cerebral autoregulation[3,15]: The intervention of the P4 is directed towards the second stage of TBI, or what is the same secondary brain injury. Since P4 recovers and improves functional performance, by inhibiting inflammation, oxidative damage, cerebral edema, and neuronal cell death[9] including many molecular mechanisms modulating inflammatory cytokines, GABAergic, and

expression of aquaporins and C5a[16]. It is likely that its pleiotropic actions are responsible for the above-observed benefits[9]. On the other hand, it is interesting that many of these inflammatory factors are the same factors that cause loss of neurons in the brain after TBI. The expression of these factors may modulate the flow of ions caused by cytotoxic TBI. However, recent studies show that on in vitro brain tissue, P4 can quickly lock multiple flow paths which modify voltage-dependent potassium channels as well as calcium channels, sodium, and GABA, and similarly, it helps to reduce the inflammatory cascade effects on a TBI[2].

4. Role of P4 in the pathophysiology of TBI

The P4 is a steroid hormone that is synthesized from cholesterol by the gonads, adrenal glands or the placenta. It can also be generated within the brain as a neurosteroid, by de novo synthesis from cholesterol or blood spot precursors metabolism[17].

For decades, the mechanism by which the P4 exerts its effects has been studied, largely attributing his actions to the classic mechanism of genomic action of steroid hormones. Neural responses caused by P4 are mediated by a series of progesterone receptor (PR) including the classic nuclear RPA and RPB and splice variants of each 7TMPR β the seven-transmembrane domain and the membrane-associated RP 25-Dx (PGRMC1). This classical PR induce regulation of gene expression. For their lipophilic properties, P4 crosses the plasma membrane of target cells and is internalized into the cytoplasm to interact with its specific intracellular receptor (HRP). Subsequently, the hormone-receptor complex binds to response elements in DNA and P4 transcription factors necessary for the polymerase to bind to the promoter and start engaging the transcription of specific genes depending on cell type[12,18]. The main function of the P4 described is linked to reproductive and immunosuppressive events. In adults, the P4 affect neuronal function by modulating transcription of genes and cellular activity through abundant classical intracellular receptors (ICR) in the CNS[19]. These receptors were characterized for the first time in 1970 and since then, they have been found in many regions of the CNS, including the hippocampus, cortex, hypothalamus, and cerebellum[20].

Like most steroids, P4 exerts its effects by binding and activating specific cell receptors. According to the common theory of steroid action, the effects of P4 are mediated by binding to its cognate receptors (RA)[20]. In the absence of hormone, the RA is complex with several chaperone molecules, including heat shock protein (PCT), PCT70, PCT40. The interaction with the accompanying RA is a prerequisite for the binding of the hormone[20]. Chaperones also serve to link the RA with protein trafficking systems. Having P4 disposition to join the RA and undergo conformational changes, dissociate chaperone proteins that then dimerize and interact directly with the elements of a specific response (ERE) in target gene promoters[21]. When P4 joins ERE, RA interacts with components of the basal transcription machinery by binding to steroid receptor co-activators. These co-activators bind to RA through a conserved amphipathic helix or LXXLL nuclear receptor-box motifs, making contact with several helices in the AF-2 (activation function) region of RA.

5. Main progesterone receptors in the CNS

Progesterone receptors are widely expressed throughout the brain regardless of specific cell types. However, expression of RA varies depending on the brain region, cell type, or hormonal of classical state-PA. Both isoforms are expressed in the hippocampus and frontal cortex of the rat. P4 is also present in norepinephrine neurons nucleus of the solitary tract, and hypothalamic supraoptic nuclei, cerebellum, hippocampus and olfactory bulb of the rat[21]. In the brain, the P4 is metabolized in neuroactive metabolites, these are the 5 DH-progesterone and 3 , 5 TH progesterone- (THP; ALLO).

There is growing evidence that neurotrophic factors have beneficial effects on cell recovery and about behavior and tissue recovery after TBI[11,22,23]. As is known, neurotrophins, also called neurotrophic factors are a family of proteins that promote the survival of neurons. These substances belong to a family of growth factors, which are a type of protein that are dumped into the bloodstream and are capable of binding to certain receptors to stimulate cell survival, growth or differentiation[2,3]. The neurotrophin family is comprised of the nerve growth factor (NGF, English, nerve growth factor), the brain-derived neurotrophic factor (BDNF, English brain-derived neurotrophic factor), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). These have important roles in neural development, axonal growth, cone guidance, neurite outgrowth, synaptic modulation, neuroprotection, and memory and behavior. In the context of the TBI, they are known trophic factors NGF and BDNF. The NGF is in cortical neurons and astrocytes were discovered by Goss and his colleagues in 1998. Under normal conditions, it helps to maintain neuronal survival through the actions of l TrkA and p75 neurotrophin receptor.24 BDNF also promotes neuronal survival, signaling through p75 and TrkB. Some researchers argue that BDNF plays an important role in synaptic modification, learning, and long-term well formation (LTP) memory, the above was discussed among research groups Greenberg in 2009, Li and Keifer, in 2012. concluding that this affects cognitive performance and long-term memory in human patients after mild TBI. Expression levels of neurotrophins and their receptors after bilateral damage to the frontal cortex was assessed trying to understand how the P4 used as treatment affects the response to injury at different duration after the initial damage[15]. Within the first three days following traumatic brain injury, P4 increased expression of NGF in the brain and this increase went hand in hand with improvements in behavioral results. Other studies have demonstrated NGF expression correlates with the recovery benefits that occur after a TBI, as is the attenuation of cell death, promoting axonal growth in the white matter, preventing further neuronal loss and inhibition of apoptosis. The above factors known at present can

be modulated by administration of P4 after a TBI[15].

Keep in mind that no event is sufficient to provide neuroprotection and neuronal repair after severe TBI. Neuroprotection processes are as complex as the own cascade of injury. Different signaling properties of P4 modify the signaling network of NGF to enhance the degree of recovery after a TBI.

6. Evidence

Exogenous progesterone protects the CNS in a variety of experimental animal models of neurodegeneration, including spinal cord injury.25 These studies dating from past decades, specifically since 1980, when evidence began to emerge that the brain is an organ steroidogenic. Baulieu et al observed steroid dehydroepiandrosterone (DHEA) and pregnenolone sulfate esters were present in higher concentrations in the brain than in circulation[26].

Noting anecdotal reports that women tend to do better recovery than men after a TBI, Stein et al, investigated the possibility that this could have a hormonal effect base to conduct a series of studies to determine if experimentally female rats with brain injury and elevated serum progesterone may suffer less neurological damage and better recovery than females with low levels of progesterone or not at the time of the injury[16]. The results of the extensive study indicate that a single injection of P4 attenuates brain edema when administered within the first 24 hours after TBI in rats, at 5 days after injection, spatial learning improved[27]. In the following analysis, Grossman et al. observed P4 reduced levels of edema, as in previous studies, however, while the accumulation of activated microglia in the brain of rats was increased TBI[28].

Progesterone inhibits the increased levels of induced injury factors C3; complement GFAP and NF-kβ factors. The paradox of double effect of P4 to induce accumulation of activated microglia and reduce immune inflammatory cytokines remains unresolved.

A randomized placebo-control trial of progesterone with or without hypothermia in patients with acute severe traumatic brain injury resulted in favour oh hypothermia an weak evidence on progesterone use[29].

6.1. Clinical studies

6.1.1. Clinical trials phase

However, the effectiveness of P4 to manage TBI; has not been proven in all the studies as recently three recent studies shown little or almost null effects of P4 treatment.30–32 Some authors believe that as expected in phase I clinical studies treatment is effective in some groups while others do not. In fact, Fee and colleagues in a 2007 study reported no benefits on the P4 after a contusion injury of the spinal cord after last 5-14 days of treatment, but observed some evidence in the gray matter, limited in the treatment groups that lasted for 14 days.33 Moreover, Gilmer et al in 2008 created a study on rats producing a “moderate” unilateral contusion of the parietal cortex and found beneficial effects after 3 days of treatment with P4.34 These authors suggested P4 could be useful in some models of injury but not all[34]. Obviously, this is a real possibility that can only be confirmed by further pre-clinical research. However, expanding the literature does not seem to support the claim that P4 as a treatment for brain injury is a failed approach also be applied in both male and female subjects. In addition, two recent studies conducted by Loane and Faden *et al.*[35,36] offer personal opinions objecting that most, if not all, studies of pre-clinical testing neuroprotective drugs, including P4 even not met set of criteria for the clinical development of new drugs.

Unless the effectiveness of a drug molecule is proven in the large clinical trial it will be difficult to mention that the drug molecule shall facilitate the complete neural repair in TBI patients[37].

6.1.2. Phase II clinical trial

In Phase II clinical studies showed clear evidence in the treatment of acute TBI with P4. In “progesterone as a treatment for TBI-Experimental Clinical Treatment”[38]. The study by the National Institute of Neurological Disorders duly randomized, double-blind, placebo control, conducted with 100 patients suffering from TBI, who were in GCS between 4-12[9,32]. The study was conducted in four groups being administered with P4 and 1 with placebo. 73% of the members of the study were male and had suffered TBI by automobile accidents.

All patients in the study were enrolled after receiving informed consent. On average, obtaining consent took about 6 hours after admission, which means that the treatment was delayed for at least 6 hours after TBI. The group receiving P4 has started an intravenous drip (IV) of 0.71 mg/kg/h for the first hour then reduced to 0.50 mg/kg/h for the next 71 h. The Safety Monitoring Board found no serious adverse events attributed to treatment. Patients in group P4 remained in a coma longer, but a reduction of more than 50% was demonstrated in mortality after 30 days compared with the control groups (placebo)[38].

Phase II results were confirmed in a study in China, 159 patients with severe TBI (GCS 8), Xiao studied in 2008, which followed patient outcomes over a longer period of up to six months[9,32]. Even in a relaxed approach, but with a different style, it is the Phase II of Duke University supported by the Department of Defense is currently studying the P4 as a precursor to treat mild TBI[9].

Despite the promising pre-clinical and clinical results, there are still issues of concern as although preclinical studies show much more benefit from the treatment and P4 as the positive results of two clinical trials are very promising, Phase III studies are needed to definitively confirm the usefulness of P4 treatment of acute TBI. Many clinical trials for stroke and TBI have failed in Phase III, which remains considerable pessimism in some quarters that a natural hormone is more successful than all the efforts of the pharmaceutical industry for over several decades.

6.1.3. P4 currently in Phase III clinical studies

Given the positive clinical phase II data [32, 33] a clinical trial sponsored by the National Institute of Health (NIH) center, Phase III, for TBI it is underway in the United States. This is a 1:01 randomized, double-blind controlled trial with 1,140 patients[9]. Treatment should begin within 4 hours of injury in patients over 18 years old with a GCS score between 12 and 4. After an IV loading dose of one hour 0.714 mg/kg, or placebo P4 administered by intravenous infusion of 0.5 mg/kg for 72 h, then kept on an additional dose of 24 h. The 4-hours-window for treatment is designed to maximize the neuroprotective effects of P4 for TBI

treatment in patients as soon as possible. The primary endpoint of the study will be a stratified dichotomy of GOS at 6 months.

In addition to the NIH study, a branch of Besins Pharma, a privately held company Belgian/ French pharmaceutical collaboration with the Brain Injury Consortium of America (ABIC) and the Brain Injury Consortium Europe (BIC) are creating a second clinical trial, approximately 1200 patients with severe TBI and GCS scores of 4-8. In whom treatment can be started within 8 hours after the injury shall be recorded in the 100-120 study through medical centers in the United States, Western Europe, Israel, Singapore, and China. Currently, there are more than 450 patients enrolled in the trial[9].

What is the next step forward?

Despite the positive results, some still argue that the results of studies of neuroprotection on P4 sound too good to be true to be a "gestational" hormonal agent that has been known for a long time in the field of physiology breeding and animal husbandry.

There are persistent stereotypes of sex hormones. Some of the more recent debates come from skeptics who argue about the value of hormone therapy in older women because the results of clinical trials were simply confused and sometimes contradictory. If P4 applications are used as treating a TBI, it should be noted that long-term treatment (over years-not days or weeks) with synthetic versions of the hormone does not always mimic the physiological effects of native P4. From a clinical perspective, an area of great concern is that progestogens are not identical to P4 as to the way they interact with the variety of mechanism, intranuclear and membrane receptors. Therefore, they should not be confused or used interchangeably in the treatment of CNS disorders, TBI or other care in the absence of assessment of safety and efficacy.

However, before this, if the two Phase III trials are successful, the P4 could become the standard treatment for acute TBI.

• There is increasing evidence that the P4 and precursors or metabolites may be useful in treating mild TBI traumatic stress disorder.

• Preclinical research of several laboratories is proving that P4 and its metabolites may be useful in treating ischemic cerebral stroke. This research is the development of data necessary to obtain FDA approval for the use of P4 in a clinical trial for ischemic injury[16].

• We must emphasize complementary treatments, such as a small but growing number of recent studies show that hormone deficiency of vitamin D (VDH) can exacerbate the result of brain injuries and strokes and for demographic reasons, many stroke victims suffer and TBI VDH deficiency. This suggests that VDH detection, along with other biomarkers of damage would be useful in the development and improvement of individualized treatments TBI or stroke[39].

• Recent studies show that supplements for VDH and P4, combined, have morphological and functional effects that produce better results than either treatment given alone.

• There are some exciting new preclinical data observing P4 can be effective in the treatment of neuroblastoma and other tumors of the CNS[40].

7. Conclusions

The neuroprotective effects of progesterone are observed during the second stage of the TBI, by modulating inflammatory cytokines, GABAergic processes, expression of aquaporin (A4) and complement factor C5a. Therefore, various forms of cellular action of progesterone mediated by a group of intracellular receptors, which includes the classical nuclear PR-A and PR-B have recognized; and splice variants of each, the 7-transmembrane domain (7TMPR β) and membrane-associated RP 25-Dx (PGRMC1). Through these receptors, progesterone induces the classical regulation of gene expression[40–45]. Although progesterone carries interesting potential effects on traumatic brain injury care, however, more studies are required to elucidate potential aspects of progesterone and allow us to clarify what well-designed studies have failed to apply[21].

Conflict of interest statement

The authors report no conflict of interest.

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