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Review Article

Hormonal therapy in traumatic spinal cord injury

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Abstract: Traumatic spinal cord injuries are major health problems and the underlying pathophysiological events and treatment strategies are currently under investigation. In this article, we critically reviewed the literature investigating the effects of estrogen, progesterone, and human chorionic gonadotropin on spinal cord damage or preservation following traumatic spinal cord injury. The National Library of Medicine database was searched through December 2016 using PubMed for articles addressing the clinical relevance of the hormones to improve neural structural integrity following traumatic spinal cord injury. It was found that each of these hormones, through varied mechanisms, could serve to reduce the harmful effects associated with spinal cord injury, and could aid in restoring some function to the injured spinal cord in the animal models. The most striking effects were seen in the reduction of inflammation commonly linked to injury of the central nervous system. The effects of human chorionic gonadotropin administration following spinal cord injury have received far less attention than those of either estrogen or progesterone, and additional inquiry could be of general benefit. In this article, we discussed the outstanding questions and suggested future directions for further investigation.

Keywords: Estrogen, progesterone, human chorionic gonadotropin, spinal cord injury, remyelination, inflammation

Introduction

Traumatic spinal cord injuries (SCI), both complete and incomplete can have devastating physiological consequences. Depending on the severity of injury, patients incur neurological deficits ranging from paralysis, loss of sensation, impaired bowel, bladder and sexual function, autonomic dysfunction and even death [1-4], and the sequelae of impairment carry with them systemic complications, including impaired wound healing, pneumonia, and ventilator dependence, to name a few. The irreversibility of SCI can be ascribed largely to the relative rarity with which axonal regeneration occurs in the adult spinal cord [5]. This lack of regeneration is attributable to glial scar formation, inflammation and cell death, dominance of inhibitory growth components, and the loss of substrates that support growth [2, 6-8].

The incidence of SCI has been demonstrated, through systematic reviews to be more prevalent in developing countries than in developed nations [9, 10], however, in the United States alone, the staggering incidence of SCI approximates to 40 injuries per million annually or about 12,400 injuries across the general population as reported in 2010 [11]. The occurrence of traumatic SCIs show a bimodal age distribution with one peak being between the ages of 15 and 29 years, and the second being above age 65 years [11, 12]. Injuries occur more often in men. The leading cause of SCI is motor vehicle accidents, followed by falls, violence (particularly gunshot wounds), and sports accidents, in descending order [13, 14]. The pronounced mobility of the cervical spine causes it to be the most commonly damaged spinal region followed by the thoracolumbar junction, which has greater mobility than that of the thoracic spine; the additional stability conferred by the ribs results in fewer traumatic thoracic injuries [10, 12].

The underlying causes of SCI vary dramatically including crush injuries, piercing injuries, vertebral herniation, and gunshot wounds. Many injuries are associated with compression, flexion, extension, distraction, axial loading or rotation of the spinal cord or column.

Table 1. Effects of hormones in relation to spinal cord injury

Hormone	Direct effect	Implications
Estrogen	Microglial activation, increased VEGF expression along with increased blood flow to site of injury, reduced calpain and caspase 3 expression, attenuated cellular calcium influx, decreased TNF-α and iNOS expression	Reduction in neuronal death, anti-apoptotic effect leading the increased cell survival, decreased inflammatory response; overall increase in preservation of function following injury
Progesterone	Downregulation of inflammatory cytokines including TNF-α and iNOS, NOS2, MCP-1, and IL-1β; downregulation of caspase 3 and GFAP	Neuroprotection due to attenuated inflammation and reduction of apoptosis; improved motor function and increased preservation of neuronal structural and functional integrity
Human chorionic gonadotropin	Reduced lesion volume in experimental stroke models	Potential improvement in functional and structural recovery following spinal cord injury

In recent years, studies have been conducted on various substances and biomolecules that could be effective in enhancing repair of the spinal cord following trauma. As a result, many promising advances have come forth in understanding the pathophysiological and biological processes involved in SCI and developing potential treatments.

Cell transplantation has been explored as a useful technique in minimizing the damage associated with SCI, and in regenerating the injured spinal cord; astrocyte transplantation has been studied in particular detail [5]. All astrocyte transplantation attempts have not provided significant benefit [15, 16]. However, recent work with embryonic glial-restricted precursor-derived astrocytes (GDAs) has proven to be effective in limiting lesion size, while also preserving white matter [17-24].

Furthermore, there have been promising advances in the delivery methods of cell and biomolecules that could improve tissue repair and regeneration in the central nervous system. Methods include encapsulated cell therapy, the use of implanted scaffolds, and biomolecule delivery in polymeric nano/microspheres and hydrogels [25]. Ji et al. observed that maintaining the integrity of the blood-spinal cord barrier following spinal cord ischemia reperfusion injury could lead to improved outcomes [26, 27].

Potential effects of immune modulatory therapies on SCI have also been examined [28]. The steroid methylprednisolone has been shown to be neuroprotective; it provides functional benefit in SCI through its action on glucocorticoid receptors, its interaction with NF-κB, and its antioxidant activity [29-35]. Inhibiting neutrophil recruitment and adhesion through targeting of the ICAM-1 and/or P-selectin has been observed to improve results in some cases of SCI [36-39], however, one study involving anti-neutrophil serum did not offer corroboratively compelling results [40]. While macrophage depletion could modestly improve outcomes following SCI [41, 42], there is a relative lack of specific methods for targeting macrophages which complicates the determination that macrophage impairment, and not another mechanism, is responsible. Despite some conflicting results [43-45] with anti-T cell methods, likewise therapies aimed at inhibiting T- and B-cells have been seen to offer some benefit [46-50]. Several anti-inflammatory therapies have been shown to provide benefit following SCI; these include the administration of anti-CD11d monoclonal antibody [51-53], the inhibition of monocytes and neutrophils together (as potential collaborators) [54], and the use of intravenous immunoglobulin [55, 56]. The antibiotic, minocycline, provides neuroprotective benefit through its ability to attenuate inflammation and apoptosis [57-69]. Some plant-derived substances such as allicin and gastrodin have also been observed to mitigate the effects of SCI through anti-inflammatory mechanisms [70, 71]. Current research is attempting to elucidate the potential benefits to be derived from mediators of inflammation.

Hormonal therapies such as those involving the administration of estrogen, progesterone, and

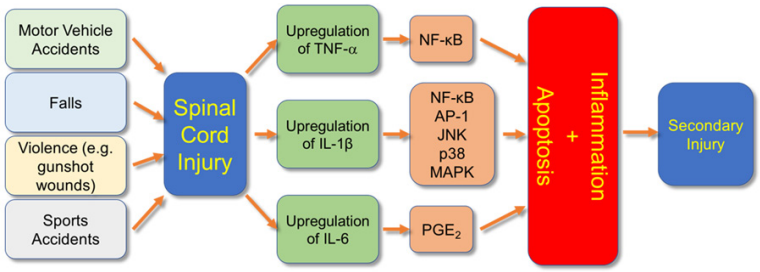

Figure 1. Schematic diagram showing underlying causes of SCI and immune response activation. Some of the major transcription factors involved in inflammatory injury following spinal cord trauma are shown. The complete signaling pathways are not depicted. Causes of SCI vary and include motor vehicle accidents, falls, violent encounters, and sports injuries. SCI is generally marked by an increase in cytokines such as TNF-α, IL-1β, and IL-6 that lead to upregulation of inflammatory and/or apoptotic agents including NF-κB, AP-1, JNK, p38 MAPK, and PGE_2. The upregulation of these factors often contributes to secondary damage which worsens the outcome following the initial injury, typically presenting as increased lesion size or increased loss of cells.

human chorionic gonadotropin (HCG) have been shown to improve outcomes following SCI (**Table 1**). These hormones act through various mechanisms that will be reviewed in this paper. The use of endogenous hormones as SCI therapy is attractive because associated results and side effects may be limited or more readily anticipated as compared to the use of some exogenous therapies. These hormones are also relatively accessible and inexpensive which improve their potential for wide-spread use.

Hormonal therapy

Historically, regeneration of peripheral nerves has been considered plausible in certain situations, however, the dogma persists that SCIs are permanently debilitating without chance of recovery. While the reality largely confirms this impression, there are areas of research in spinal cord regeneration that are demonstrating tremendous promise. Areas that have been recently explored include cell transplantation, steroid hormone administration, immune modulatory therapies, and the administration of inflammation suppressants and other biomolecules among others. This review will focus on the hormones, estrogen, progesterone, and HCG and their effects on the injured spinal cord.

Estrogen

Many pharmacological agents and their effects following traumatic spinal cord injury have been studied [72-75]. Among these, estrogen has been shown to exhibit a neuroprotective effect [76-79]. This effect is a result of anti-inflammatory processes and activation of varied serine proteases by estrogen [76]. Letaif et al. [80] note that this anti-inflammatory activity is perpetrated through microglial activation, increased blood flow to the site of injury, increased levels of anti-apoptotic proteins, attenuated cellular influx of calcium following injury and administration of estrogen [81-83]. In fact, increased estrogen levels may be partially responsible for improved outcomes in females relative to males following SCI [84].

The overexpression of cytokines has been observed following injury of the central nervous system [85, 86]. Upregulation of genes expressing cytokines such as tumor necrosis factor-a (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) has been observed shortly following SCI [87-92] (**Figure 1**). TNF-α mediates inflammatory processes through its activation of NF-κB, which in turn upregulates other pro-inflammatory cytokines [93-97]. Pishva et al. [98], determined that administration of estrogen twice daily following SCI in rats significantly reduced the gene expression of TNF-α and its downstream cytokine iNOS and this likely accounts for at least some of the inhibitory effect estrogen has on inflammation following SCI (**Figure 1**).

While estrogen may not be effective in returning complete function and mobility to an individual following traumatic spinal cord injury, it has been shown to improve functional scores in studies performed in rats [80]. However, between weeks four and six following the induced injury, the group administered a single dose of 17b-estradiol intraperitoneally scored significantly higher than their control counterparts with mean BBB scores being reported as 15.1 for the estradiol group and 9.3 for the control by week 6, which was statistically significant [80]. Hubscher et al. [99] likewise reported improved scores through the sixth

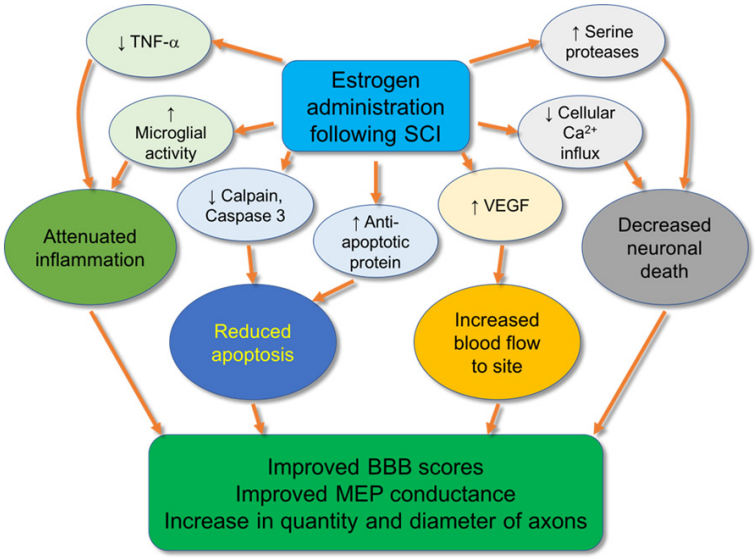

Figure 2. Compared to SCI controls, subjects receiving estrogen injections following injury exhibit reduction in TNF-α, increased microglial activity, reduced calpain and caspase 3 levels, increased levels of anti-apoptotic protein, decreased cellular calcium influx, increased serine protease activation, and increased VEGF expression. This, in turn, leads to attenuated inflammation, decreased apoptosis, and increased blood flow to the site of injury, resulting in improved scores on the Basso-Bresnahan-Beattie (BBB) scale for locomotion, improved conduction velocity on motor evoked potential (MEP) monitoring, and increased quantity and diameter of axons.

week of their experiment. Other studies reviewed cover a short period and only provide insight into the initial effects of estrogen following SCI [76]. While Ritz and Hausmann reported lower BBB scores after the fourth week [77], other groups have reported significant improvements in BBB scores in estrogen-treated rats earlier than the fourth week [76, 78]. The conflicting findings underscores the importance of a potential benefit with additional long-term studies extending well beyond the fourth week to clarify our understanding of the effects of estrogen on functional nervous system scores, beyond the short-term. Moreover, some investigators have administered estradiol in multiple doses [76, 78, 83] and observed good cellular and physiological results. Olsen et al. [83] administered estrogen for the first 21 days following SCI. The studies employing multiple dosing schedules [76, 78] reported earlier improvements in BBB scores compared to those that administered a single dose [80] (**Figure 2**).

In addition, large differences between treatment and control animals have been seen using motor evoked potential monitoring (MEP) [80]. In this test, latency, or the time taken for an electrical impulse to travel from the head to the limbs, and the amplitude of the transmitted impulse were measured. Letaif et al. [80] reported a 17-fold increase in the speed of travel of the electrical impulse in estrogen-treated rats as compared to the control, and a 7-fold increase in the amplitude of same impulse. The strictly objective nature of this test makes it a valuable and evaluative tool for measuring neural function. Thus, MEP proves indispensable in future studies involving injuries of the nervous system in evaluating the effect of treatment (**Figure 2**).

No significant improvement has been observed from a histological perspective in rats treated with estrogen following SCI when analyzed for necrosis, hemorrhage, hyperemia, axon degeneration, and cellular infiltration. However, there has been a marked increase in quantity and diameter of axons observed in rats treated with estrogen compared to control [80]. The mean number of fibers for the estradiol group was reported as 92.6 and that of the control group was 56.9 which was statistically significant. Whereas the mean diameter of axons for the estradiol group was 92.4 compared to a mean of 55.1 for the control group, which was again, statistically significant [80].

So far, studies examining the effects of estrogen injection following SCI have administered the treatment directly following the injury. This provides useful insight into the results of early treatment with estrogen. However, it would be of benefit to directly compare the effects of early administration with later administration to ascertain any differences in benefit that exist. In fact, Sribnick et al. found that chronic cases of SCI are also amenable to estrogen therapy and exhibit improvements in motor function following treatment [78]. The effect on chronic cases could be further explored.

It has been shown that some molecules that bind the estrogen receptors such as G-1, tamoxifen, and other estrogen receptor agonists, can have neuroprotective functions similar or identical to those of estrogen following SCI [100-108]. High dose estrogen administration has not become a standard of care for SCI patients in large part due to the adverse effects associated with estrogen levels well above normal physiological levels. These side effects include increased rates of deep vein thrombosis and cancer [109, 110], and the development of feminine physical traits in males. Samantaray et al. [1] reported that low dose estrogen administration attenuates gliosis and provides protection for neurons in the caudal penumbra following traumatic SCI in rats. It was observed that low dose estrogen administration (5-10 μg/kg) 48 hours following the injury resulted in the attenuation of inflammatory events, reduced calpain expression which induced an anti-apoptotic effect, reduced caspase-3 expression also inhibiting apoptosis, increased expression of the estrogen receptors ER-α and ER-β (suggesting effects relate to increased receptor signaling), attenuated neuronal death, and increased expression of VEGF which is a potent stimulator of vasculogenesis and angiogenesis. Apart from the increased expression of estrogen receptors, the observations failed to exhibit any significant difference between the 10 μg and 100 μg doses of estrogen.

Thus, the research findings to date suggest that low dose estrogen administration and estrogen receptor agonists exhibit potential to be further explored in animals, and in clinical trials in humans following additional knowledge on potentially adverse effects. Estrogen has been shown to ameliorate SCI, but the undesirable effects associated with high-dose estrogen administration limit its potential as a standalone therapy.

Progesterone

Progesterone (PROG) is a steroid hormone produced by the ovaries and placenta in females, and by the adrenal glands in both females and males. The nervous system has the capacity to locally synthesize PROG and convert PROG into its active metabolite, allopregnanolone [111]. As with estrogen, PROG has been shown to be promyelinating, anti-inflammatory, and neuroprotective in cases of nervous system injury [112-115]. When studied in relation to brain trauma, PROG was shown to prevent neuron loss and mitochondrial dysfunction, reduce edema and inhibit inflammatory cytokines, as well as, improve motor function on diagnostic scales [116-118]. Moreover, PROG has also been tested in two Phase II clinical trials which suggested its efficacy as a treatment option for traumatic brain injury patients [119-121]. With respect to SCI, PROG has been shown to prevent chromatolysis, preserve motor neuron structure, upregulate the expression of choline acetyltransferase and brain-derived neurotrophic factor (BDNF), which increase production of acetylcholine and help to support preservation, growth, and differentiation of neurons, respectively. PROG has also been shown to reduce the proliferation and activation of astrocytes and microglia, and increase the production of oligodendrocyte progenitor cells [113, 122-124]. PROG could be a target for therapies aimed at improving neural function following injury by modulation of astrocytes and their pathogenesis [125]. As was observed with estrogen, 10 μg/kg/12 h PROG administration significantly reduced the expression of TNF-α and iNOS genes following SCI, which lead to production of inflammatory mediators and nitric oxide (NO) which can contribute to reactive radical damage [126]. Garcia-Ovejero et al. [127] observed comparable effects following SCI in rats administered PROG subcutaneously each day. After 60 days, there was a marked increase in spared white matter (SWM) preservation in PROG-treated rats compared to control with white matter measurements of 58.60 ± 4.06% and 22.99 ± 3.03% volume, respectively, as measured 2.5 mm rostrally and caudally from the epicenter of contusion. However, there was no significant difference in the volume of spared gray matter (SGM) observed between control rats and those treated with PROG. Increased oligodendrocytes, decreased myelin damage, improved axonal preservation, and improved locomotor function were all demonstrated following the administration of PROG after SCI.

While another study recapitulated the improved motor and histological outcome with PROG administration [128], the beneficial results are not universal: Fee et al. [129] found no improvement with PROG injection following SCI. Part of this discrepancy could be a result of

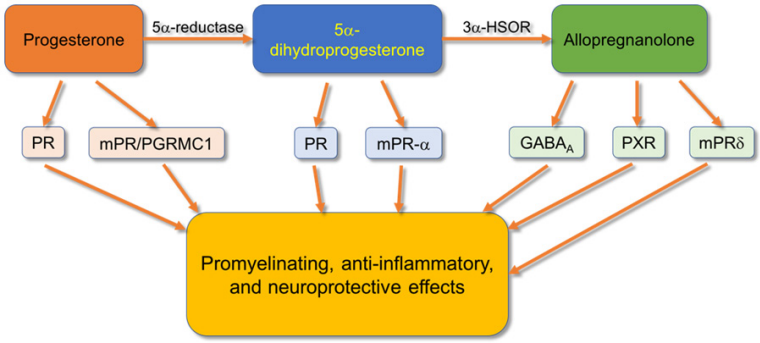

Figure 3. Compared to SCI controls, subjects receiving progesterone injections following injury exhibit reduced expression of TNF-α and subsequently iNOS, increased acetylcholine production and neuron growth through upregulation of choline acetyltransferase and brain-derived growth factor (BDNF), downregulation of NOS2, MCP-1, IL-1β, caspase-3, and GFAP. Observations have been noted of decreased chromatolysis, increased preservation of neuron structure, and a reduction of mitochondrial dysfunction in animals administered progesterone following SCI. It has been noted that progesterone and its metabolites 5a-dihydroprogesterone and allopregnanolone act on those receptors depicted to contribute to the mediation of the effects listed. In this schematic diagram, complete pathways are not depicted, but some of the major components are shown.

differences in the duration of study, as reported observations in the study of Fee et al. [129] were limited to 5 days as opposed to 60 days and 6 weeks in the studies producing positive results.

Guennoun et al. [111] found the binding of progesterone to intracellular progesterone receptors (PR) via its classical pathway, and it may also bind to specific membrane sites (mPR/PGRMC1 complex) to activate intracellular signaling pathways (**Figure 3**). Moreover, allopregnanolone may act on GABA$_A$ receptors following its conversion from PROG [111, 130-135]. They also determined that PROG acted on the effectors PR, mPRs, and PGRMC1. After conversion to 5a-dihydroprogesterone through a mechanism involving 5a-reductases, action occurred on the effectors PR and mPRa (**Figure 3**). Following conversion via 3a-HSOR to allopregnanolone (3a5a-THPROG), it can bind to GABA$_A$ receptors, PXR, and mPRd to induce neuroprotective effects [111] (**Figure 3**). Further understanding of the receptors upon which PROG and related molecules act could prove useful in developing treatments aimed at neuroprotection. Future work is required to ascertain potential side effects associated with synthetic progestins and allopregnanolone as many synthetic progestins may also bind androgen and glucocorticoid receptors producing undesirable effects [136, 137], and allopregnanolone has been associated with some cognitive impairment and symptoms such as anxiety, irritability, aggressiveness, seizure, and increased pain [138-142]. Of note, it has been determined that PR reduces reactive gliosis and preserves oligodendrocyte precursor cells in the injured spinal cord in rats [143].

PROG shows potential as a modulator of neuropathic pain following SCI [144-146]. While there may be many mechanisms by which pain is transmitted following central nervous system injury [147, 148], neuro-inflammation and reactive gliosis are primary causes of chronic pain following SCI [149-151]. Cytokines are involved in the modulation of neuronal function and pain transmission [151-156]. Coronel et al. [144] explored the effects of PROG on IL-1β and its receptors IL-1RI and IL-1RII, antagonist IL-1ra, IL-6, TNF-α, and NR1 subunit of N-methyl-D-aspartate receptor (NMDAR) following SCI. IL-1β, IL-6, and TNF-α mRNA (and protein) levels were significantly lower in rats receiving PROG than the placebo, on the first day status post injury; however, there was only a significant difference in mRNA levels observed on day 14 in IL-1β, and no significant difference on day 28 of the study. There was no significant difference in IL-1RI mRNA levels between the groups on days 1 or 14, but by day 28, the PROG-treated group had significantly lower levels than the placebo. IL-1RII mRNA levels were seen to be markedly higher in the PROG group on day one, with no significant difference thereafter. No differences were observed between the two groups in IL-1ra mRNA levels. These data as well as those showing fewer IL-1RI positive neurons in the spinal cords of PROG-treated rats compared to those receiving placebo suggest that PROG may provide benefit to those experiencing chronic pain following SCI, but may not have the same effect or mediate it in the same way in the immediate aftermath of the injury. Additional research on the effect of PROG following SCI, with a focus

on IL-1RI, and its utility as a treatment option in cases of chronic pain following SCI, is warranted. There is indication that the effect of PROG could differ in acute and chronic settings.

Yang et al. [157] observed that PROG significantly reduces axonal dieback and neuronal death in mice following SCI when observed at intervals of 24 h, 48 h, and 72 h from the initial injury. This was mediated via down-regulation of inflammatory cytokines, including NOS2, MCP-1, and IL-1β as well as activated caspase-3 and GFAP. Interestingly, upregulation of myelin basic protein (MBP) was also noted. It was also suggested that PROG improved behavioral function following SCI. Further studies of a longer duration would help elucidate the effects of PROG on axon and neuron preservation beyond the acute stages.

PROG is effective as an anti-inflammatory agent that can improve motor function and histological outcomes following SCI. To date, the side-effects associated with PROG are not as immediately apprehensible as those of some others, and it continues to exhibit potential as an effective treatment following injury of the central nervous system.

HCG

Human chorionic gonadotropin (HCG) is a heterodimer consisting of an α and a β subunit, which are non-covalently linked. The hCGa subunit constitutes part of other hormones such as luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. HCG is produced in the adrenal pituitary gland by gonadotropin cells [158, 159].

HCG presents potential as a treatment in the case of central nervous system injury. It was observed in a preliminary study that HCG helped to increase the amount of adrenal medulla tissue survival following autologous transplant in the lateral ventricles of rat brains [160]. Proliferation of endogenous stem cells in the subgranular zone and the subventricular zone has been observed to increase with administration of HCG [161]. Meng et al. [162] observed that HCG induced neuronal differentiation of PC12 cells by activating the stably expressed lutropin/choriogonadotropin receptor in vitro. In a study of rats with experimental strokes, treatment with HCG + erythropoietin (EPO) significantly reduced the lesion volumes (by 82-89%) and significantly improved neurological scores compared to three other treatment groups including HCG + saline, saline + EPO, and saline + saline [163]. This would also suggest that EPO may play a role in the reduction of lesion size following stroke.

Extensive literature reviews illustrate a relative void in research performed using HCG in association with SCI as compared with studies using estrogen and progesterone. Patil and Nagaraj [164] found that 12 rats receiving HCG injections following SCI exhibited a significant improvement in functional recovery (assessed by measurement and grading of the return of bladder function and the ability to climb up an inclined plane) within 6 weeks as compared to 10 rats serving as control. In a later study, Patil et al. [165] transected the spinal cords of 21 rats at the midthoracic level; the 11 rats administered HCG exhibited significantly increased amplitudes of the cortical evoked motor action potentials after six weeks compared to the control group. These findings suggest that the administration of HCG may serve to improve spinal cord function following traumatic injury. However, the relatively small number of animals studied and the limited number of retrievable studies of the effects of HCG on individuals with SCI preclude any conclusive determinations of universal effectiveness or possible side effects until further research is undertaken.

HCG may act to improve motor function and minimize neuronal damage following spinal cord lesion. The minimal side effects associated with HCG, and the relative lack of research that has been performed on its effect on SCI mandate further investigation as a potential therapeutic option.

Conclusion

Estrogen, progesterone, and HCG are hormones with diverse functions that could serve to attenuate the harmful consequences of SCI through their abilities to interact with the GABA system, reduce excitotoxicity, free radicals, edema, and apoptosis, inhibit inflammatory cytokines, induce increased angiogenesis, mitochondrial recoupling, remyelination [166], and induce stem cell migration to the site of injury. These functions have potential to

improve prognoses for individuals suffering after SCI with promise of increased motor function, preserved structure, and a reduction of neuropathic pain. Further investigation into each of these methods is of paramount importance.

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Disclosure of conflict of interest

None.

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