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Review

Sex steroids and neuroprotection in spinal cord injury: A review of preclinical investigations

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ABSTRACT

Spinal cord injury (SCI) is a debilitating condition that affects motor, sensory and autonomic functions. Subsequent to the first mechanical trauma, secondary events, which include inflammation and glial activation, exacerbate tissue damage and worsen functional deficits. Although these secondary injury mechanisms are amenable to therapeutic interventions, the efficacy of current approaches is inadequate. Further investigations are necessary to implement new therapies that can protect neural cells and attenuate some of the detrimental effects of inflammation while promoting regeneration.

Studies on different animal models of SCI indicated that sex steroids, especially 17β-estradiol and progesterone, exert neuroprotective, anti-apoptotic and anti-inflammatory effects, ameliorate tissue sparing and improve functional deficits in SCI. As sex steroid receptors are expressed in a variety of cells including neurons, glia and immune system-related cells which infiltrate the injury epicenter, sex steroids could impact multiple processes simultaneously and in doing so, influence the outcomes of SCI. However, the translation of these pre-clinical findings into the clinical setting presents challenges such as the narrow therapeutic time window of sex steroid administration, the diversity of treatment regimens that have been employed in animal studies and the lack of sufficient information regarding the persistence of the effects in chronic SCI. The current review will summarize some of the major findings in this field and will discuss the challenges associated with the implementation of sex steroids as a promising treatment in human SCI.

Contents

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Introduction

Traumatic spinal cord injury (SCI) is a debilitating condition that can lead to permanent neurological disability. It is estimated that approximately 273,000 people live with SCI in the United States and the annual incidence is about 12,000 new cases per year (NSCISC—www.uab.edu/nscisc). Major causes of SCI include traffic and sport accidents, falls and violence. SCI is most common among young adults with an incidence rate that is 3–4 times higher in male than female subjects (DeVivo, 2012). However, increased incidence among elderly females, primarily due to falls, has been reported (Furlan et al., 2005). In addition to loss of locomotor function, affected individuals suffer from secondary co-morbidities such as chronic pain, spasticity, and bladder, bowel and sexual dysfunction.

The initial traumatic event that elicits tissue destruction in the injured spinal cord is followed by cellular and molecular changes which occur within hours to weeks and cause further damage to the spared tissue. The secondary events include activation of glia, infiltration of immune system-related cells, induction of inflammation, secretion of detrimental effectors that cause neuronal and oligodendrocyte death and demyelination. The formation of a cavity and the glial scar at the injury epicenter and the molecular milieu at the lesion site constitute major impediments to the regeneration of transected axons and remyelination of spared, intact axons. Yet, these secondary injury mechanisms are amenable to treatment and could be targets of therapeutic interventions that modulate inflammation, promote neuroprotection, enhance regeneration and reinstate function. Despite many medical advances, the current therapies have limited efficacy and do not effectively alleviate neurological deficits or adequately restore function.

Studies on animal models have shown gender differences in functional outcomes of SCI, with remarkably better locomotor recovery in female than male rodents (Farooque et al., 2006; Hauben et al., 2002). These findings, together with investigations reporting beneficial effects of 17β-estradiol and progesterone in animal models of brain injury and disease (for reviews see Brown et al., 2009; Deutsch et al., 2013; Herson et al., 2009), spurred interest in the neuroprotective roles of sex steroids in SCI (Kwon et al., 2011). Yet, controversy exists on gender-differences in individuals with SCI. Greenwald et al. (2001) did not find gender-related differences in Functional Independence Measure (FIM) motor scores or American Spinal Injury Association (ASIA) scores at acute care admission or rehabilitation discharge. In individuals with incomplete tetraplegia, no significant gender differences were noted in motor and sensory neurologic recovery at the time of admission, rehabilitation discharge or during the follow-up years (Pollard and Apple, 2003). Co-morbidities, mortality, discharge disposition and neurologic outcomes were not significantly different in men and women with similar cervical SCI, although women showed a trend for higher incidence of reactive depression and venous thrombosis (Furlan et al., 2005). In contrast, a multi-center study on a large number of individuals with SCI indicated gender differences in certain (but not all) neurologic scores. Whereas the mean motor index scores at admission and 1 year post-injury were not statistically different in women and men with SCI, the degree of neurologic improvement, evaluated as the difference between motor index scores at 1 year post-injury and at admission, was significantly better in women than in men sustaining complete or incomplete SCI (Sipski et al., 2004). However, when FIM motor scores were analyzed, in general, men functioned better than women at the time of rehabilitation discharge. Finally, no significant differences were observed in the neurologic recovery of pre- and post-menopausal women with SCI. However, a definite conclusion could not be reached due to the lack of information about estrogen replacement therapy in post-menopausal women sustaining a SCI.

The aim of this review is to provide an overview of the animal studies that assessed the effects of sex steroids in SCI. We will start by presenting a brief description of the various animal models, the functional outcome measures and the histopathological parameters that are frequently used in investigations of SCI. Subsequently, we will summarize some of the findings related to the effects of sex steroids in animal models of SCI. Finally, we will discuss the challenges associated with the translation of the pre-clinical studies into the clinical setting.

Animal models of SCI, functional outcome measures and histopathological parameters

Evaluation of therapeutic strategies that promote functional recovery following SCI necessitates the use of clinically relevant animal models and reliable outcome measures that reproducibly assess motor, sensory and autonomic functions. A number of methods have been used to induce SCI in rodents (Rosenzweig and McDonald, 2004; Onifer et al., 2007). As the majority of injuries in humans are the result of a blunt trauma, animal models of contusive injury are increasingly accepted as paradigms mimicking the human condition. Different devices such as the New York University (NYU) (Gruner, 1992) or MASCIS impactor (Young, 2002), the Ohio State University (OSU) impactor (Bresnahan et al., 1987; Noyes, 1987) and the Infinite Horizon SCI device (Rabchevsky et al., 2003; Scheff et al., 2003) are used to perform contusion injuries in rodents. Compression of the rat spinal cord with an aneurysm clip (Fehlings and Tator, 1995; Rivlin and Tator, 1978), forceps crush injury in rodents (Plemel et al., 2008; Zhang and Guth, 1997) and complete or incomplete transection injury, including dorsal and lateral hemisection, have also been utilized (Onifer et al., 2007; Rosenzweig and McDonald, 2004).

Open field locomotor function in rats and mice that sustain thoracic injury is often assessed by use of the Basso, Beattie and Bresnahan (BBB) rating scale for rats (Basso et al., 1995) and the Basso Mouse Scale (BMS; Basso et al., 2006). The modified Tarlov Scale (Gale et al., 1985), originally developed by Tarlov and Klinger (1954), has also been used to assess motor movement in rats sustaining SCI. Additional tests have been designed to evaluate motor function in rats with cervical SCI (Martinez et al., 2009; Webb and Muir, 2005). The *CatWalk* gait analysis assesses parameters of locomotion including stride characteristics (Hamers et al., 2006). In addition, the grid walk test, the inclined plane test (Muir et al., 2007) and the horizontal ladder test (Soblosky et al., 2001) assess motor or sensorimotor function. The hotplate paw withdrawal test and the Von Frey hair test are frequently used to measure thermal and mechanical hypersensitivity, respectively (Mills et al., 2001). At the histopathological level, the most prevalent measurements are lesion volume and spared white or gray matter (Basso, 2004). Tissue sparing has been correlated with recovery of locomotor function (Basso, 2004).

Sex steroid receptor signaling and expression in the spinal cord

In this review, we will focus on actions of sex steroids which are achieved by plasma levels encountered in males or females during physiological/supra-physiological situations including stress and pregnancy: concentrations below 0.1 μM for estrogens or androgens and below 1 μM for progesterone (for a review see Nicot, 2009). Sex steroids exert both genomic and non-genomic actions through receptors