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INVITED REVIEW

Give progesterone a chance

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Abstract

There is currently no standard pharmacological treatment for spinal cord injury. Here, we suggest that progesterone, a steroid hormone, may be a promising therapeutical candidate as it is already for traumatic brain injury, where it has reached phase II clinical trials. We rely on previous works showing anti-inflammatory, neuroprotective and promyelinating roles for progesterone after spinal cord injury and in our recent paper, in which we demonstrate that progesterone diminishes lesion, preserves white matter integrity and improves locomotor recovery in a clinically relevant model of spinal cord lesion.

Key Words: *spinal cord injury; myelin; trauma; neuroprotection; progesterone*

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Spinal cord injury (SCI) usually leads to devastating deficits that produce a strong impact on patients, their families and their communities. Neural damage may cause loss of sensory and motor capabilities (paraplegia or tetraplegia), infections, loss of bladder and bowel control, cardiac and respiratory dysfunctions and the development of neuropathic pain (Baptiste and Fehlings, 2006; Silva et al., 2014).

Unfortunately there is currently no standard pharmacological treatment for this condition, even though some molecules have shown protective effects in experimental animal models and some have entered the first stages of clinical trials (Kwon et al., 2011; Rabchevsky et al., 2011; Lammertse, 2013). Only methylprednisolone reached an extended clinical practice, but re-evaluation and the accumulated expertise have raised serious concerns about its real effectiveness and safety (Hurlbert, 2001, Bracken, 2012), and the use of this compound is being reduced in some countries (Schroeder et al., 2014).

Traumatic brain injury (TBI) is a pathology that shares many pathological features with traumatic SCI. In TBI, like in SCI, several therapeutical approaches have been followed, including high dose methylprednisolone, but none of them has become a gold standard for acute care (Margulies et al., 2009; McConeghy et al., 2012). In the last years, progesterone (PROG), a steroid hormone, has arisen as a strong candidate. PROG is widely known by its role in reproduction but also shows neuroprotective properties in different paradigms of brain lesion: reduces brain edema, moderates inflammation and preserves neurons and glial cells (Guo et al., 2006; Cutler et al., 2007; Stein, 2008, 2011). Because of the promising experimental and preclinical results obtained, PROG could be a pharmacological "golden bullet" for patients with severe TBI (Beauchamp et al., 2008) and, indeed, it has been used in two clinical trials that will enter shortly in phase III (Wright et al., 2007; Xiao et al., 2008).

In SCI, the enthusiasm about PROG has been much more limited, even though PROG shows neuroprotective and remyelinating effects (De Nicola et al., 2009; Schumacher et al., 2012). In this pathology, we previously demonstrated that PROG restores the normal levels of choline acetyltransferase (ChAT) and neuronal Na, K-ATPase, enhances the expression of growth-associated protein GAP-43 and BDNF, prevents the lesion-induced chromatolytic degeneration of spinal motoneurons (Labombarda et al., 2002; Gonzalez et al., 2004), increases the expression of pro-oligodendrogenic genes (Labombarda et al., 2009) and decreases reactive gliosis (Labombarda et al., 2011).

The curbed impact for progesterone in SCI may be due to the lack of consensus on the functional effects that follow anatomical and histological improvements (Thomas et al., 1999; Fee et al., 2007). A closer look to published works shows some features that may underlie this discrepancy: 1) The intensity of the lesion used is not exactly the same: the study showing motor improvements used a moderate/severe injury (Thomas et al., 1999), while the study showing no effects used a less severe injury (Fee et al., 2007); 2) PROG treatment was limited in these studies to the first days after the lesion; and 3) in the study describing no effects of PROG on locomotion, motor evaluation was discontinued in the subacute phase of the lesion (21 days after injury), long before a plateau is reached in locomotor recovery (Basso et al., 1995; Scheff et al., 2003).

In contrast, literature and our own experience suggest that, 1) the use of a variety of complementary motor tests is recommended when studying gait and locomotion in treated rats, mostly if subtle changes are expected, like those observed in mild to moderate injuries; 2) a long-lasting treatment may be required to observe PROG effects (Labombarda et al., 2009, 2010, 2011); and 3) long survival times of treated animals (beyond 30–60 days) are frequently required to observe behavioural effects derived from the histological improvements induced by the treatment.

For these reasons, and based on our previous data, we decided to evaluate the functional effects of a chronic PROG treatment on rats submitted to a clinically relevant model of SCI: a moderate/severe thoracic contusion (200 kdyn, no dwell time), in which rats survived until the chronic phase (60 days after injury) (Garcia-Ovejero et al., 2014). In that paper, we studied anatomical and histological parameters using MRI, histochemistry, immunohistochemistry and stereology. We also studied motor function on a weekly basis, using a visual open field-based locomotor scale (Basso-Bresnahan-Beattie scale for locomotion, score and subscore; Basso et al., 1995; Basso, 2004), and an automated gait analysis system (Catwalk® , Hamers et al., 2001).

First, we determined the effect of PROG on the extension of the lesion 60 days after injury both by T2W-3D MRI and histology, showing that PROG reduced the volume and the length of the lesion. This was accompanied by a notable increase in white matter preservation at the epicenter from 7% found in vehicle treated SCI animals to 16% preservation in PROG treated rats. Previous studies have shown that a small increase in spared white matter may result in a substantial recovery of locomotor function, probably by preserving more supraspinal and propiospinal inputs (Basso et al., 1996; Schucht et al., 2002; Kloos et al., 2005). PROG also increased oligodendrocyte numbers in the lesion epicenter, maintaining up to 35% of the total number of oligodendrocytes *versus* the 7.5% observed in vehicle treated rats. This also was accompanied by a higher expression of myelin basic protein. Additionally, PROG preserved a higher number of axonal profiles at the epicenter.

Second, we studied locomotor function of the injured rats. We found a notable improvement in many parameters of locomotion induced by PROG, like the recovery of forelimb and hindlimb coordination, that is lost in rats after a thoracic spinal cord trauma (Basso et al., 1996; Kloos et al., 2005; Koopmans et al., 2005; Hamers et al., 2006), indicating a better functional connection between lumbar and cervical motor control centers, that underlies a coordinated gait (Pearson and Rossignol, 1991; Barriere et al., 2008). Another parameters that PROG improved, points to a more efficient locomotion: less trunk instability, less hindpaw rotation, better toe clearance, a decrease in the base of support (distance between the hind paws during locomotion), an increase in the swing phase (time that the hindpaw was not in contact with the glass floor), and an increase in the stride length. These parameters normally change in the opposite direction after SCI, and have been explained as adaptations to an instable gait (Hamers et al., 2001, 2006; Joosten et al., 2004; Hamers et al., 2006; Hendriks et al., 2006).

Treatments that produce beneficial effects after SCI might eventually present also undesired effects. For this, we checked if our treatment also conveyed a development of mechanical allodynia or thermal hyperalgesia. We did not find any of those phenomena in tests involving dynamic Von Frey aesthesiometry (Dolan and Nolan, 2007), Hargreaves test (Hargreaves et al., 1988), and CatWalk parameters normally decreased in animals developing allodynia (Deumens et al., 2007; Vrinten and Hamers, 2003).

Therefore, PROG is a molecule that induces long-term tissue preservation and improves functional outcome after spinal cord contusion when administered in an appropriate dose and frequency. For this, and attending to the good safety results described for PROG in brain clinical trials (Wright et al., 2007; Xiao et al., 2008), we think that, among the different possible treatments that remain in a preclinical phase, PROG may be a good candidate to show effectiveness in SCI as it is doing so far in TBI. Respectfully, all we are saying is give progesterone a chance…

Conflicts of interest: *None declared.*

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