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COMMENTARY

Spasticity therapy reacts to astrocyte GluA1 receptor upregulation following spinal cord injury

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For almost three decades intrathecal baclofen therapy has been the standard treatment for spinal cord injury spasticity when oral medication is ineffective or produces serious side effects. Although intrathecal baclofen therapy has a good clinical benefit-risk ratio for spinal spasticity, tolerance and the life-threatening withdrawal syndrome present serious problems for its management. Now, in an experimental model of spinal cord injury spasticity, AMPA receptor blockade with NGX424 (Tezampanel) has been shown to reduce stretch reflex activity alone and during tolerance to intrathecal baclofen therapy. These results stem from the observation that GluA1 receptors are overexpressed on reactive astrocytes following experimental ischaemic spinal cord injury. Although further validation is required, the appropriate choice of AMPA receptor antagonists for treatment of stretch hyperreflexia based on our recent understanding of reactive astrocyte neurobiology following spinal cord injury may lead to the development of a better adjunct clinical therapy for spasticity without the side effects of intrathecal baclofen therapy.

LINKED ARTICLE
This article is a commentary on Oshiro *et al.*, pp. 976–985 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2010.00954.x

Abbreviations
ITB, intrathecal baclofen treatment; SCI, spinal cord injury

Spasticity following spinal cord injury (SCI) has been operationally defined as an increase in velocity-dependent tonic stretch reflexes (muscle tone) and exaggerated tendon jerks to passive movement (Taylor *et al.*, 1997; 1999; Adams and Hicks, 2005), although the functional impact of other clinical symptoms such as cutaneous flexor hyperreflexia and spasm activity may equally contribute to this syndrome (Hiersemenzel *et al.*, 2000; Adams and Hicks, 2005; Bennett, 2008; Gómez-Soriano *et al.*, 2010). Intrathecal baclofen therapy (ITB) is the standard treatment for spasticity following SCI, when oral medication is found to be ineffective at maximum doses or presents serious side effects (Dario and Tomei, 2004; Adams and Hicks, 2005). Although ITB therapy has a good benefit/risk profile for spinal spasticity (Dario and Tomei, 2004), baclofen tolerance has been observed in up to 22% of patients (Dario and Tomei, 2004; Heetla *et al.*, 2009) and cases of a life-threatening withdrawal syndrome have been reported (Dario and Tomei, 2004; Mohammed and Hussain, 2004; Adams and Hicks, 2005). Systemic baclofen treatment may also lead to excessive muscle weakness affecting the residual motor capacity below the incomplete SCI, which directly affects the ability of the patient to walk or stand (Dario and Tomei, 2004; Adams and Hicks, 2005).

The study by Oshiro *et al.* (2010) in this issue of *BJP* is important because it demonstrates that AMPA antagonists may also be effective for the field of spasticity management following SCI, particularly during ITB tolerance, and possibly for treatment of the baclofen withdrawal syndrome. Using the clinically relevant model of spasticity after ischaemic SCI, the authors show that both systemic and intrathecal blockade of AMPA receptor function with NGX424 (Tezampanel) reduces stretch reflex

activity and compensates for ITB tolerance. Furthermore voluntary motor disruption with this treatment was found to be minimal, suggesting that AMPA receptor antagonism may have an added benefit, in view of the clinical reports of baclofen-induced muscle weakness (Dario and Tomei, 2004). The choice of AMPA receptor blockade for experimental spasticity control is not new, as NBQX has been shown to decrease excessive hind/limb electromyographic and H reflex activity in an experimental genetic model of spasticity in the rat (Turski *et al*., 1992). However, the authors were motivated to investigate the potential of NGX424 for spasticity control following their previously published observation of an increase in GluA1 receptors on astrocytes following ischaemic SCI (Hefferan *et al*., 2007), which may explain the efficacy of NGX424 to inhibit stretch reflex activity (Oshiro *et al*., 2010). Indeed, the application of spinal GluA1 antisense molecules decreases stretch reflex activity after SCI, and greatly reduces the expression of this receptor on both astrocytes and to a lesser degree on motoneurones (Hefferan *et al*., 2007).

Although not extensively discussed by Oshiro *et al*. (2010), the blockade of AMPA receptors following SCI may also constitute an alternative rescue treatment strategy for ITB withdrawal syndrome, which usually results from mechanical problems of the delivery device or from an empty reservoir (Dario and Tomei, 2004). Fortunately the frequency of ITB withdrawal syndrome in patients with spasticity is usually low in centres with experience of these devices (Dario and Tomei, 2004; Mohammed and Hussain, 2004). Within 1–2 days after cessation of baclofen treatment, the symptoms of ITB withdrawal syndrome is characterized by a return to spasticity and rigidity, which can develop to include fever, seizures, loss of consciousness, renal and hepatic failure and sometimes death (Dario and Tomei, 2004). If ITB treatment is restarted the symptoms improve over 24–72 h, but often benzodiazepine adjunct therapy has to be used in the meantime (Dario and Tomei, 2004). As such systemic AMPA receptor treatment may alleviate some of the symptoms of baclofen withdrawal syndrome, up to the time that ITB therapy can be re-instated, and therefore, may provide another pharmacological strategy for the clinician to reduce and manage the development of these serious life-threatening symptoms.

The treatment of other symptoms of spasticity, such as involuntary muscle spasms (Gómez-Soriano *et al*., 2010) or cutaneous hyperreflexia (Hiersemenzel *et al*., 2000; Bennett, 2008) was not assessed with NGX424 administration by Oshiro *et al*., (2010). Previously, the AMPA antagonist NBQX was found to be ineffective in the reduction of flexor reflex activity in the genetic rat model of spasticity (Turski *et al*., 1992), but this contrasts with electrophysiological data that describe the action of this antagonist as reducing substantially, both mono and polysynaptic ventral root reflex activity, and the synaptic activation of motoneurones in the intact spinal cord (Farkas and Ono, 1995). As such, the application of AMPA receptor antagonists may also be effective in reducing cutaneous hyperreflexia and involuntary muscle contractions, symptoms which often have a greater effect on the daily activities of patients with SCI spasticity (Bennett, 2008; Gómez-Soriano *et al*., 2010). In addition, there is some evidence to suggest that AMPA receptor antagonists only minimally affect locomotor activity (Turski *et al*., 1992), and this is supported by the transient motor effect observed with NGX424 in animals with spasticity by Oshiro *et al*. (2010). The development of pharmacological agents capable of reducing a wide range of spasticity symptoms while preserving residual voluntary motor function should be an important clinical goal for sub-acute rehabilitation of patients with incomplete SCI.

Administration of the AMPA receptor antagonist NBQX shortly after contusion spinal cord injury in the rat has been shown to protect the gray matter adjacent to the lesion area, leading to a degree of functional recovery of hind/limb reflexes and locomotor function one month later (Wrathall *et al*., 1997). It is possible, therefore, that administration of AMPA antagonists within a clinically relevant time frame would also promote some recovery of functional motor activity while reducing symptoms of spasticity. The study by Wrathall *et al*. (1997) also showed an increase in 5-HT immunoreactivity below the SCI in rats treated with NBQX. We have previously shown that stretch hyperreflexia develops following a lesion of the dorsolateral funiculus, suggesting that descending disinhibition may in part mediate some symptoms of spasticity (Taylor *et al*., 1999, see Figure 1). Taken together these results suggest that the development of a pharmacological treatment strategy for spasticity should be directed to promote neuroregeneration of descending inhibitory motor pathways when possible, across the incomplete SCI, while reducing both local glutamate receptor overexpression and glial reactivity (Figure 1).

Although further experimental validation of the action of NGX424 for spasticity treatment is required, particularly in relation to the duration of its effect on stretch hyperreflexia in addition to minimizing its effect on general motor function, the clinical use of this antagonist may constitute an important alternative adjunct therapy for spasticity

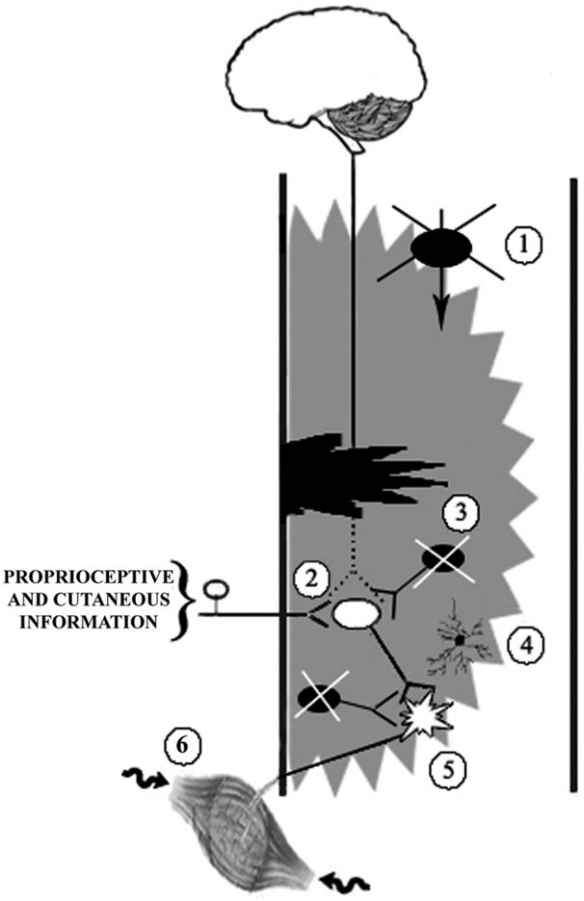

Figure 1

Schematic representation of the key pathophysiological mechanisms of spinal cord injury spasticity and the role of local GABAergic disinhibition and astrocyte GluA1 receptor over-expression below the primary lesion site (black area) within the area of secondary lesion (gray area). Disruption of descending inhibitory pathways (1) following experimental spinal cord injury leads to stretch reflex hyperreflexia (Taylor *et al.*, 1999). Spinal cord injury may also lead to excessive muscle hyperreflexia (6) in response to both proprioceptive and cutaneous afferent input (2) following disinhibition of local GABAergic control at the pre and post synaptic site (3). Astrocyte GluA1 overexpression (4) following experimental ischaemic spinal cord inury (Hefferan *et al.*, 2007) has now been identified as an important therapeutic target for reduction of stretch reflex activity following administration of NGX424 (Tezampanel) as monotherapy or during baclofen tolerance (Oshiro *et al.*, 2010). However, the action of NGX424 at other synaptic sites, such as within the dorsal horn (2) or directly upon the motoneurone (5), cannot be excluded. Development of an experimental therapy capable of promoting regeneration of descending inhibitory pathways (1) while reducing glutamate receptor overexpression and reactive gliosis (4) within the injured spinal cord should be particularly effective for the management of a wide range of spasticity symptoms in the future.

in those patients with ITB treatment (Oshiro *et al.*, 2010). NGX424 has been used in the clinic, although it can produce side effects of sedation and dizziness after systemic administration (Oshiro *et al.*, 2010). At the experimental level, it remains to be shown whether AMPA antagonists that reduce excessive stretch reflex activity can also modulate other symptoms including cutaneous hyperreflexia and involuntary spasm activity. In addition, this study suggests that a wide range of spasticity symptoms may develop as a result of neuroinflammation. Pro-inflammatory cytokines directly modulate both AMPA and GABA induced currents in dorsal horn lamina II neurones, as has been observed with TNF-α and IL-6 (Kawasaki *et al.*, 2008), which suggest that pharmacological agents for spasticity therapy should also be focused on neuroinflammation control. Finally, and as previously mentioned by the authors (Hefferan *et al.*, 2007), the action of AMPA antagonists on stretch reflex activity as a direct result of GluA1 blockade on astrocytes, rather than at a neuronal site, needs to be identified and differentiated. However, we can now expect that the development and appropriate choice of glutamate receptor antagonists for the treatment of the spasticity syndrome, based on our recent understanding of reactive astrocyte neurobiology following SCI, will lead to more effective therapeutic strategies and better clinical management of secondary side effects associated with ITB treatment.

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Conflicts of interest

The author declares no known conflict of interest in this work.

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