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Commentary: Immunohistochemical comparison of astrocytic mGluR5 upregulation in infraorbital nerve- versus sciatic nerve-ligated rat

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Neuropathic pain is described as a pain caused by nerve injury or disease that affects the somatosensory system. It is the most difficult to treat, available treatments such as antidepressants, anticonvulsants and opioids have a relative efficacy and dose limiting side effects. Understanding the underlying mechanisms of neuropathic pain is critical to find more efficient and more tolerable treatments.

In the past two decades, neuroinflammation has been shown to play an important role in the development and the maintenance of neuropathic pain. Central neuroinflammatory processes are mainly mediated by two glial cells, microglia and astrocytes, which inhibition reduced neuropathic pain[1-3]. However, depending on the type of neuropathic pain, glial inhibitors have differential efficacy that would be related to different neuroinflammatory mechanisms. It was shown that neuropathic pain induced by anticancer drugs involves neuroinflammatory processes mediated by astrocytes but not microglia[4], on the contrary neuropathic pain induced by nerve constriction involves both astrocytes and microglia activation[3]. Moreover, depending on the nerve injured, glial inhibitors have differential effects; propentofylline, which inhibit both astrocytes and microglia activation, reduced pain in L5 spinal nerve ligation model but was totally inefficient to reduced pain after crush of tibial and peroneal nerves[1,5].

Similarly, our previous works showed that neuropathic pain affecting the trigeminal system have specific pharmacological and physiopathological characteristics compared to pain affecting the spinal system[3,6]. Using models of chronic constriction injury of either the infraorbital nerve (trigeminal system) or the sciatic nerve (spinal system) we showed that the time course of pain development and the pain duration are different in these models[7]. We also showed a differential overexpression of the neuroinflammatory mediators interleukin-6 and brain-derived neurotrophic factor[3,8], suggesting that mechanisms underlying glial activation are different after infraorbital nerve ligation or sciatic nerve ligation. Indeed, the microglial inhibitor minocycline, reduced neuropathic pain in sciatic nerve ligated rats but was inefficient in trigeminal nerve ligated rats[3]. Because commonly used glial inhibitors are non-selective drugs, which effects on glial cells is poorly understood and depends on the type of neuropathic pain, studies aiming at understand specific mechanisms underlying glial dysregulation are particularly important in the pain field.

Among glial cells involved in neuroinflammatory processes, astrocytes are particularly important in the regulation of neuronal communication. Astrocytes uptake glutamate form the synaptic cleft and release neurotransmitters such as glutamate and D-serine. Previous studies showed that neuroinflammatory mediators participate to neuronal sensitization through a downregulation of glutamate transporters activity in astrocytes which was mediated by the metabotropic glutamate receptor 5 (mGluR5)[9].

In a recent paper[10], we investigated modifications of the astrocytic mGluR5 expression in models of infraorbital nerve ligation compared to sciatic nerve ligation. mGluR5 was overexpressed in both the trigeminal nucleus of infraorbital nerve ligated rats and the spinal cord of sciatic nerve ligated rats. Both mRNA and protein levels were increased in nerve injured animals, indicating that mGluR5 upregulation is caused by changes in gene expression, although we can not exclude that post-transcriptional regulation may be involved.

Moreover, mGluR5 upregulation paralleled the overexpression of the astrocyte marker glial fibrillary acidic protein (GFAP). Evaluation of mGluR5 and GFAP colocalization showed, in control animals, that mGluR5 is partially expressed in astrocytes, indicating the presence of two astrocyte populations differing in their expression of mGluR5. In contrast, in rats that underwent ligature of the infraorbital nerve or the sciatic nerve, the majority of GFAP-immunoreactive cells stained positive for mGluR5. These data are in line with other studies that showed an upregulation of mGluR5 in astrocytes after spinal nerve compression[11] and suggest that mGluR5 overexpression would participate to neuropathic pain mechanisms in both infraorbital nerve and sciatic nerve ligation models.

However, we evaluated the expression of mGluR5 in astrocytes only on day 7 after surgery, a time point for which we previously showed that GFAP overexpression reach a peak in both infraorbital nerve and sciatic nerve ligated rats[3,12]. The evaluation of a single time point, raises the question of the relation between mGluR5 overexpression and pain. Although pain symptoms are fully developed 14 days after infraorbital nerve and sciatic nerve ligation, mechanical hypersensitivity develops progressively after nerve injury and is already significantly different from sham animals on day 7 after sciatic nerve ligation[7]. In infraorbital nerve ligated rats, the time course of pain development is delayed compared to sciatic nerve ligated rats and mechanical hypersensitivity is significantly different to sham animals from day 12 post-surgery. However, evaluation of mechanical sensitivity, which is the easiest and the most used method to assess pain behavior in infraorbital nerve ligated rats, give an incomplete information concerning pain symptoms induced by a nerve injury. Vos et al.,[13] who first characterized the model of infraorbital nerve ligation, described modifications of spontaneous behavior, such as unilateral face grooming on the territory innervated by the injured nerve, starting on day 3 post-surgery. Although face grooming in animal can also be associated with itch, exacerbated face grooming is a pain symptom well characterized in pain models induced by injection of proinflammatory mediators in the facial area[14]. Thus, these data suggest that mGluR5 overexpression on day 7 after nerve injury would participate to the development of neuropathic pain in both infraorbital nerve and sciatic nerve ligated rats.

In this study, we showed similarity regarding mGluR5 expression in infraorbital nerve and sciatic nerve ligated rats, however, it is worth mentioning we also show a difference in mGluR5 overexpression in these models. While mGluR5 was upregulated only in the ipsilateral spinal cord after sciatic nerve ligation, infraorbital nerve ligation induced a mGluR5 upregulation in both ipsilateral and contralateral trigeminal nucleus. Whether this overexpression is associated with bilateral pain induced by infraorbital nerve ligation was not evaluated and further investigations should help to clarify the role of mGluR5 in trigeminal neuropathic pain.

In conclusion, the upregulation of mGluR5 in astrocytes after either infraorbital nerve or sciatic nerve ligation would be a common physiopathological mechanism involved in the development of neuropathic pain affecting the trigeminal and the spinal system. This should be considered for the development of new drugs against neuropathic pain with different characteristics. This work also highlights that comparison of different pain models is of importance to find physiopathological mechanisms that are specific or common to various neuropathic pain and identify new therapeutic targets.

Conflicts of interest: none declared

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