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Editorial comment

Complex role of peroxisome proliferator activator receptors (PPARs) in nociception

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1. Peroxisome proliferator activator receptor (PPAR) signalling

In this issue of the *Scandinavian Journal of Pain*, Okine et al. report the analgesic action of the synthetic peroxisome proliferator activator receptor-alpha (PPARα) agonist WY-14643 on nociceptive spinal neuronal firing in a rodent model of neuropathic pain [1]. The search for an efficient treatment of neuropathic pain has been rather challenging and the demonstration that new targets can be found is very encouraging. PPARα is a very promising target because contrary to many other anti-nociceptive treatments, its activation does not seem to be associated with any undesirable effect but rather is linked to several more broad benefits. It has been for instance, associated with lowering of inflammation [2], and improvement of cognitive functions in models of cognitive impairment [3]. Moreover, it was also shown not to induce tolerance, which is a common problem in chronic pain treatment [4].

The peroxisome proliferator-activated receptors (PPARs) are nuclear receptors best characterized for their actions in metabolism and oxidative stress regulation. The PPAR family includes PPARα, PPARβ/δ and PPARγ all of which are expressed at different levels by microglia, astrocytes, neurons and oligodendrocytes [5]. PPARs heterodimerize with the Retinoid X receptor to bind DNA on the PPAR response element (PPRE) and initiate gene transcription [6], several co-factors like PGC1-alpha, CBP/p300, SERC1 are necessary for further fine-tuning of tissue-specific effects. PPRE is highly conserved in different species, suggesting a fundamental role for the pathways it activates in a variety of fundamental biological processes. In addition to these genomic effects, receptor-like almost instantaneous responses (within minutes), independent of gene activation have also been described (reviewed in [7]), consistent with the earlier finding that a fraction of the PPARα proteins is located at the cell membrane [8]. This novel observation added even more complexity to the previous canonical vision on genomic PPAR signalling.

The field of PPAR signalling has been rapidly expanding following the discoveries of endogenous ligands and the development of new subtype specific agonists but, till recently, it has been mostly directed to the study of metabolic and vascular disorders [9].

2. PPARα in nociception

It has been found recently that PPARα also plays an important anti-nociceptive role in the nervous system [4], which is clearly demonstrated in PPARα knockout mice, by their enhanced sensitivity to a range of noxious and mechanical stimuli in neuropathic pain models [10].

This likely implies that PPARα is an activator of endogenous pathways involved in limiting excessive pain signalling. The endogenous PPARα agonist palmitoylethanolamide is able to activate and subsequently desensitize the pain transducing TRPV1 channels in the peripheral nociceptive sensory neurons [11]. This study and others also suggests that the anti-nociceptive effect is mediated via the rapid, non-genomic PPARα signalling pathway. All these data present PPARα as a multifaceted candidate pathway for the fine-tuning of pain control. To date, much attention was paid to the role of PPAR in primary sensory neurons (peripheral nociception), which express a plethora of pain transducing molecules such as heat and capsaicin activated TRPV1 receptors.

Recent study by Okine et al. [1] adds new support for the role of PPARα in pain control and identifies novel spinal targets for pain processing. The authors show that intraperitoneal administration of the synthetic PPARα agonist WY-14643 attenuated key symptoms of neuropathic pain in rats. The authors also obtained original data suggesting, unlike previous views on the peripheral role of PPARα [8], the involvement of spinal neurons in nociceptive signal processing in spinal nerve ligation model of neuropathic pain. The principal significance of the latter relies on the rationale route of drug administrations to counteract spinally located neuropathic pain. Effective systemic administration of analgesic drugs targeting central or spinal neurons normally protected by the brain–blood barrier has an obvious advantage over intrathecal delivery. The synthetic PPARα agonist WY-14643 used in this study is also

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