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Commentary

Central sensitization needs sigma receptors

Sigma receptors were originally thought to represent a class of opioid receptors that are activated by the prototypic benzomorphan SKF-10,047 (N-allylnormetazocine) [8]. However, later studies and the molecular cloning of the receptor demonstrated that the two receptor subtypes, sigma 1 (σ1R) and sigma 2 (σ2R), represent unique transmembrane proteins without any homology to opioid receptors or other mammalian proteins [5].

Nevertheless, σ1Rs modulate opioid analgesia and they also play an important role in pain modulation that is not regulated by the endogenous opioid system. The latter aspect of σ1R signaling has been investigated in several recent studies using selective antagonists of σ1Rs, as well as of σ1R knockout mice [7]. Both experimental strategies produced essentially the same results. The absence of functional σ1Rs resulted in a marked attenuation of pain responses in the formalin test and completely abolished capsaicin-induced mechanical hypersensitivity [1,3,4,10]. Further, the expression of σ1Rs was up-regulated after peripheral nerve injury on the ipsilateral side of the spinal cord and the nerve injury-induced development of mechanical hyperalgesia was blocked by σ1R antagonists [10].

To this interesting set of data, De la Puente and her co-workers now add a further piece of the puzzle by looking at neuropathic pain conditions after partial sciatic nerve ligation in the σ1R knockout mouse model. In their study they observed a profound reduction of mechanical and cold plate hyperalgesia induced by nerve injury in the knockout animals, while thermal hyperalgesia remained intact [2]. Importantly, they substantiated the behavioral data with *in vitro* electrophysiological recordings from spinal cord tissues and demonstrated that wind-up responses after stimulation of the dorsal root were reduced in knockout mice. Their manuscript thus adds to the converging evidence, which implicates σ1R in the modulation of spinal pain sensitization.

On the molecular level, a picture emerges whereby σ1Rs modulate the activity of spinal NMDA receptors that regulate plastic adaptations associated with central sensitization [6]. Thus, a number of σ1R ligands showing no affinity for NMDA receptors were found to modulate NMDA-induced Ca^{2+} influx and NMDA-induced neuronal activity [9]. The effects of σ1Rs, which are mostly localized in the endoplasmatic reticulum, are probably indirect through the regulation of inositol 1,4,5-trisphosphate (IP_3)-dependent Ca^{2+} mobilization and subsequent activation of Ca^{2+}-dependent phosphatases, such as protein kinase C and ERK [5]. In good agreement with this proposed molecular mechanism, De la Puente et al. found that ERK phosphorylation in the dorsal horn was stimulated by the neuropathic pain condition in wild-type mice, but not in animals lacking σ1Rs. The signaling cascade eventually feeds back on the NMDA receptor by increasing the expression and phosphorylation status of its NR1 subunit. This increase is also stimulated by σ1R agonists and blocked by σ1R antagonists [6].

It should be noted that the spinal NMDA-mediated sensitization processes show many similarities to long-term potentiation in the hippocampus. One can thus assume that the molecular mechanisms of antipsychotic drugs acting on higher brain functions via σ1Rs also are very similar.

Nowadays it seems to be a common practice to propose any molecule involved in a pathological process as a potential drug target for treatment in the concluding statement of the study, and the paper of De la Puente et al. is no exception. Unfortunately, it may be too early to raise such a hope. So far it has only been shown that blocking σ1R function before and during the experimental insult can attenuate or even block the typically resulting hyperalgesia. The demonstration that σ1R antagonists have any efficacy in reverting central sensitization and thereby in reducing the increased pain sensitivity is still missing.

If the modulation of NMDA receptor activity (and perhaps of other ion channels) is the main function of σ1R signaling in the process of central sensitization, it may in fact be too late to antagonize σ1Rs after the deed is done. In that case, σ1R antagonists might only work at a very early stage of the disease process. However, considering the good safety profile of existing drugs such as haloperidol [3], an application may be useful as a preventive measure for a well-defined group of patients.

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