Intra-thalamus injection of ZD7288 reduced nociceptive behavior in rats

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Introduction

The thalamus is the brain structure that receives projections from multiple ascending pain pathways and relays nociceptive input to the cortex and the limbic system. Human imaging study suggests thalamic dysfunction in neuropathic pain [1]. However, the molecular basis underlying the chronic pain mediated thalamic dysfunction in ascending pain pathway remains unclear. Considerable evidence indicates that dysfunction of Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activity is associated with the development and maintenance of chronic pain and inhibition of HCN channel activity produces anti-nociceptive effect [2-3]. We hypothesized that increased HCN activity in the thalamus contributes to the chronic pain. We found that HCN immuno-reactivity is increased in the thalamus of rats with chronic pain and inhibition of HCN activity ameliorates mechanical allodynia and thermal hyperalgesia in rats with neuropathic pain or monoarthritis.

Materials and methods (NA for case report)

Adult male Sprague–Dawley rats weighing 250-270 g were anesthetized with pentobarbital (50 mg/kg, i.p.). Chronic constriction injury (CCI) to sciatic nerve was performed and Complete Freud’s adjuvant (CFA) or saline was injected into one side of the ankle articular cavity. A guide cannula was subsequently implanted in the ventral posterior lateral nucleus (VPL) of the thalamus contralateral to the injury or CFA injection side. Mechanical allodynia and Thermal hyperalgesia was assessed using the foot-withdrawal test. Immediately after the observation of behavior, Immunostaining and Western blot were carried out.

Results/Case report

Rats subjected to unilateral CCI exhibited mechanical allodynia and thermal hyperalgesia in the ipsilateral hindpaw as compared to sham controls (Fig. 1A and B). Both 1 µg and 5 µg of ZD7288 infusion attenuated mechanical allodynia and the effect of 5 µg of ZD7288 lasted for 90 min (Fig 1C and E). Thermal hyperalgesia was also reduced after the ZD7288 infusion in CCI rats and the higher ZD7288 dose (5 µg) did not further enhance the effect (Fig 1D and F). ZD7288 infusion also produced a prolonged anti-nociceptive effect on the hindpaw ipsilateral to CFA injection. By fourteen days after CCI and CFA, protein expression and immuno-reactivity of both HCN1 and HCN2 were increased in the contralateral thalamus as compared with that of sham rats analyzed by Western blot (Fig. 2A) and immunohistochemistry (Fig. 2B).

Discussion

Accumulating evidence suggests that abnormal HCN channel activity contributes to the development and maintenance of chronic pain. But the role of the thalamic HCN channel activity in chronic pain condition remains unknown. Our data suggest that HCN channel activity in the thalamus contributes to the behavioral manifestation of chronic pain in two rodent models without changing thermal or mechanical nociceptive threshold in sham rats. The VPL nucleus is a major relay site of the spinothalamic track for pain and temperature sensation, our data show that inhibition of HCN channel activity in the VPL nucleus alleviated chronic pain. While the exact mechanisms by which HCN channel activity in the thalamus regulates chronic pain remains to be examined, The present results suggest that searching for HCN subtype blockers relevant for pain would be beneficial to patients with chronic pain.

References (Maximum 5)


Tables/images

Figure
Figure 2

Disclosures

I declare that there are no conflicts of interest or support that may cause bias in my presentation.