Brain Res Bull. 2014 Jul;106:47-55. doi: 10.1016/j.brainresbull.2014.05.005. Epub 2014 Jun 18.

Hydrogen-rich saline controls remifentanil-induced hypernociception and NMDA receptor NR1 subunit membrane trafficking through GSK-3β in the DRG in rats

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PMID: 24951883 DOI: 10.1016/j.brainresbull.2014.05.005

Abstract

Background: Although NMDAR trafficking mediated by GSK-3β involvement in transmission of pronociceptive messages in the spinal cord has been confirmed by our previous studies, whether NMDAR trafficking is implicated in peripheral sensitization remains equivocal. It is demonstrated that inflammation is associated with spinal NMDAR-containing nociceptive neurons activation and the maintenance of opioid induced pain hypersensitivity. However, whether and how hydrogen-rich saline, as an effective anti-inflammatory drug, could prevent hyperalgesia through affecting peripheral sensitization caused by NMDAR activation remains to be explored.

Methods: To test these effects, hydrogen-rich saline (2.5, 5 or 10 ml/kg) was administrated intraperitoneally after remifentanil infusion, NMDAR antagonist MK-801 or GSK-3β inhibitor TDZD-8 was administrated intravenously before remifentanil infusion in rats. We examined time course of hydrogen concentration in blood after hydrogen-rich saline administration. Mechanical and thermal hyperalgesia were evaluated by measuring PWT and PWL for 48 post-infusion hours, respectively. Western blotting and real-time qPCR assay were applied to analyze the NR1 membrane trafficking, GSK-3β expression and activity in DRG. Inflammatory mediators (TNF-α, IL-1β, and IL-6) expressions in DRG were also analyzed.

Results: We found that NR1 membrane trafficking in DRG increased, possibly due to GSK-3β activation after remifentanil infusion. We also discovered that hydrogen-rich saline not 2.5 ml/kg but 5 and 10 ml/kg could dose-dependently attenuate mechanical and thermal hyperalgesia without affecting baseline nociceptive threshold, reduce expressions of inflammatory mediators (TNF-α, IL-1β, and IL-6) and decrease NR1 trafficking mediated by GSK-3β, and minimal effective concentration was observed to be higher than 10 μmol/L, namely peak concentration in arterial blood after administration of HRS 2.5 ml/kg without any influence on hyperalgesia.

Conclusion: Our results indicated that antihyperalgesic effect of hydrogen-rich saline might depend predominantly on its ability to reverse NR1 trafficking via inhibition of GSK-3β activity in DRG in a dose-dependent manner.

Keywords: DRG; GSK-3β; Hydrogen-rich saline; NR1; Opioid-induced hyperalgesia.

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