Activation of Xc- by N-acetyl-cysteine inhibits Nociceptive Responses in Humans

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We recently found that pharmacological activation of type-2 metabotropic glutamate receptors (mGlu2) *via* N-acetyl-cysteine (NAC), an activator of cystine/glutamate anti-porter (System Xc-) causes analgesia in mouse models of inflammatory or neuropathic pain. NAC acts by reinforcing the endogenous activation of mGlu2 receptors, as demonstrated by the evidence that NAC-induced analgesia was abrogated in mice lacking mGlu2 receptors or by the mGlu2/3 receptor antagonist, LY341495 (Bernabucci, 2012). Here we extended the study of NAC to healthy human volunteers. For the analysis of nociceptive responses we recorded (i) the large and stable component of the lower limb reflex (RIII reflex) following electric stimulation of the sural nerve and (ii) the laser-evoked potentials (LEPs) generated in cortical region of the pain matrix. A numeric rating scale (NRS) was also used for the assessment of the subjective pain perception. This was a double-blind cross-over study in which ten human volunteers (age: 20-30 years) were treated with NAC (1.2 g, p.o.) and placebo with at least one week of interval. All subjects underwent analysis of pain responses under basal conditions and then 1 hour following the administration of NAC or placebo. We found that NAC was able to significantly increase the threshold of RIII reflex and reduce the amplitude of N1 and N2P2 LEPs, which reflect responses generated by secondary somatosensory cortex/insular cortex and insular network/anterior cingulate cortex, respectively. NAC was also effective in reducing NRS score in the same subjects. We also examined the action of NAC on acute nocifensive response in mice using the tail-flick test. A single injection of NAC (100 mg/kg, i.p.) caused a robust analgesia in mice, and its action was abrogated by co-injection with LY341495 (1 mg/kg, i.p.), as expected. The strategy of reinforcing the endogenous activation of mGlu2 receptors can be successfully applied to the treatment of pain. These data lay the groundwork for the study of NAC in patients with chronic pain.

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