

Neuroinflammation and pain

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentlig försvaras i Arvid Carlsson salen, Academicum, Medicinaregatan 3, Göteborg, fredagen den 26 september 2014, kl 13:00

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Avhandlingen baseras på följande delarbeten:

- I. Forshammar J, Block L, Lundborg C, Biber B, Hansson E (2011) Naloxone and ouabain in ultralow concentrations restore Na^+/K^+ -ATPase and cytoskeleton in lipopolysaccharide-treated astrocytes. *J Biol Chem* 286:31586-31597.
- II. Block L, Forshammar J, Westerlund A, Björklund U, Lundborg C, Biber B, Hansson E (2012) Naloxone in ultralow concentration restores endomorphin-1-evoked Ca^{2+} signaling in lipopolysaccharide pretreated astrocytes. *Neuroscience* 205:1-9.
- III. Block L, Björklund U, Westerlund A, Jörneberg P, Biber B, Hansson E (2013) A new concept affecting restoration of inflammation-reactive astrocytes. *Neuroscience* 250:536-545.
- IV. Block L, Lundborg C, Bjersing J, Dahm P, Hansson E, Biber B. Ultralow dose of naloxone as an adjuvant to intrathecal morphine infusion improves perceived quality of sleep in patients with severe, long-term pain. A randomized, double-blind, placebo-controlled study. Submitted.



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ABSTRACT

Background: Persistent pain that remains long after the physiological trigger has been resolved is a disabling condition. A possible mechanism for the transition from acute physiological pain to persistent pain involves low-grade inflammation in the central nervous system, in which inflammatory-activated astrocytes play a significant role.

Aims: The aims of this thesis were to explore novel means for the restoration of inflammatory-activated astrocytes and to investigate whether such experimentally obtained findings, when translated into a clinical setting, are associated with improved pain relief in patients with persistent pain.

Methods: For the experimental studies in cell cultures, Ca^{2+} imaging, Western blot analysis, immunocytochemistry, and enzyme-linked immunosorbent assay (ELISA) were performed. In the clinical study, patients were treated with continuous intrathecal infusions of morphine in combination with naloxone or a placebo.

Results: Inflammatory-activated astrocytes were restored to their normal state and function using a combination of the μ -opioid agonist endomorphin-1, ultralow doses of naloxone, and the antiepileptic drug levetiracetam. For patients with persistent pain who were treated with an ongoing intrathecal morphine infusion, the addition of an ultralow dose of naloxone significantly improved their perceived quality of sleep.

Conclusion: We demonstrated that astrocyte dysfunction, which occurs as a component of low-grade neuroinflammation during prolonged pain states, is experimentally restorable by the combined actions of morphine, naloxone, and levetiracetam. To achieve this response, the choice of an ultralow dose of naloxone seems to be particularly crucial. Additionally, our findings in patients with difficult-to-treat pain show that intrathecal administration of an ultralow dose of naloxone in combination with morphine significantly improves perceived quality of sleep, although concurrent alterations in pain relief were not statistically significant. The concept of targeting inflammatory-activated astrocytes to reduce the development of persistent pain is a promising path that merits further evaluation in clinical settings.

Keywords: Persistent pain, neuroinflammation, astrocytes, morphine, naloxone, intrathecal administration

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