

Central nervous modulation of pain -a clinical and experimental study

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska Akademin
vid Göteborgs Universitet kommer att offentligen försvaras i Hjärtats Aula, Sahlgrenska
Universitetssjukhuset, Göteborg, fredagen den 30 oktober 2009, kl 09.00

av
Christopher Lundborg
Leg läk

Fakultetsopponent:
Docent Märta Segerdahl
Avdelningen för Anestesiologi och Intensivvård
Karolinska Institutet, Stockholm, Sverige

Avhandlingen baseras på följande delarbeten:

- I. Lundborg C, Dahm P, Nitescu P, Biber B.
High intrathecal bupivacaine for severe pain in the head and neck
Acta Anaesthesiol Scand. 2009, 53: 908–913
- II. Lambert G, Elam M, Friberg P, Lundborg C, Gao S, Bergquist J, Nitescu P.
Acute response to intracisternal bupivacaine in patients with refractory pain of the head and neck
J Physiol. 2006, 570: 421–428
- III. Lundborg C, Hahn-Zoric M, Biber B, Hansson E.
Glial cell line-derived neurotrophic factor is increased in cerebrospinal fluid but decreased in blood during long-term pain
Submitted
- IV. Lundborg C, Westerlund A, Björklund U, Biber B, Hansson E.
Naloxone, IL-1ra and ifenprodil restore GDNF-evoked Ca²⁺ transients in inflammatory reactive astrocytes
Submitted

Göteborg 2009



UNIVERSITY OF GOTHENBURG

Central nervous modulation of pain -a clinical and experimental study

Christopher Lundborg

Department of Anesthesiology and Intensive Care Medicine, Institute of Clinical Sciences at
Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Abstract:

This series of studies addresses several conceptual issues in modern pain therapy related to the contemporary understanding of mechanisms and modulators involved in the pain sensation. Novel invasive therapy for severe pain, neurogenic interactions, humoral regulators and cellular responses were studied.

Methods: I) Continuous intrathecal (IT) bupivacaine administration at intracisternal or high cervical levels in patients with severe refractory pain, II) Isotope-dilution techniques for analysis of baroreflex responses and catecholamine release in this patient group, III) Differential analysis of activities of cytokines, including glial cell line-derived neurotrophic factor (GDNF), in intrathecal and blood compartments in patients with long-term pain due to osteoarthritis, and IV) Co-cultivation of astrocytes for imaging and quantification of changes in Ca²⁺ signalling when activated by pro-inflammatory lipopolysaccharide (LPS) and interleukin-1 β (IL-1 β).

Results and conclusions: I) For patients with severe pain in areas innervated by cranial and upper cervical nerves not responding to conventional pharmacological pain therapy, cervical high spinal analgesia is a valuable and safe option with clinical good results, II) Acute administration of intracisternal bupivacaine is associated with increases in systemic blood pressure and heart rate as a result of substantial augmentation of efferent reflex sympathetic nervous activity. We propose this reflects a bupivacaine-induced reduction of afferent baroreceptor discharge to the brain stem, III) Long-term pain is associated with increased levels of GDNF in cerebrospinal fluid (CSF), but decreased levels in blood and simultaneously increased levels of pro-inflammatory cytokines in CSF and blood, and IV) LPS and the cytokine IL-1 β attenuate GDNF-induced Ca²⁺-signalling in co-cultured astrocytes, and induce conformational changes of the cytoskeleton. Naloxone and ifenprodil restore LPS-attenuated Ca²⁺-transients, and naloxone also restores the conformational changes of the cytoskeleton.

Key words: Head and neck, pain, cisterna magna, baroreflex, noradrenaline, GDNF, osteoarthritis, co-cultured astrocytes, naloxone, calcium

ISBN 978-91-628-7885-6