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Nitric Oxide Synthases and Soluble Guanylyl Cyclase in Spino-Parabrachial and Spino-Periaqueductal Projection Neurons of Lamina I of the Rat Spinal Dorsal Horn.

Geboren am 04.10.1976 in Frankfurt am Main
Staatsexamen am 03.06.2005 an der Universität Heidelberg

Promotionsfach: Anatomie und Zellbiologie
Doktorvater: Prof. Dr. med. Klaus Unsicker

The full expression of inflammatory and neuropathic pain in animal models is both dependent on spinal production of nitric oxide (NO) and on the functioning of spinal lamina I neurons that express the neurokinin receptor 1, most of which project to the brainstem. Long term potentiation (LTP) at nociceptive synapses is a cellular model for the central sensitization involved in many forms of chronic pain. Consistently, lamina I neurons with a projection to the periaqueductal gray (PAG) show LTP after conditioning stimulation of primary afferent C-fibres, and this LTP is NO-dependent. To elucidate possible sources and sites of action of NO in LTP at spino-PAG neurons, we immunohistochemically examined the localization of the neuronal, endothelial and inducible nitric oxide synthases (nNOS, eNOS, and iNOS respectively) and the NO-receptor soluble guanylyl cyclase (sGC) in lumbar spinal cord of young rats. Neuronal NO synthase was rarely encountered in lamina I neurons (2%), including spino-PAG neurons (1%). Endothelial and inducible NO synthase were found only in the vasculature of spinal cord. In contrast, sGC was widely expressed in neurons of the spinal cord, i.e., 53% of all lamina I neurons and 89% of the spino-PAG neurons expressed sGC. Furthermore lamina I spino-parabrachial neurons, that show a NO-independent LTP, exhibited nNOS- and sGC-expression comparable to that of spino-PAG neurons. These results suggest that NO may be generated in neighbouring neurons or blood vessels and acts on the spino-PAG neuron and/or the primary afferent C-fibre to enable LTP. Also nNOS may only be localized at synapses with C-fibers, inaccessible for immunostaining with the applied methods, but in close vicinity to N-methyl-D-aspartatic acid receptors and sGC, forming signaling micro-domains for spatially confined NO signal transduction.