ABSTRACT

Pathological pain states linked to several diseases or tissue damage are often associated with increased sensitivity to stimuli. The main underlying mechanisms of this hypersensitivity are peripheral sensitization of nociceptors and central sensitization in the spinal cord. One of the crucial processes of central sensitization is the modulation of synaptic transmission at the dorsal horn of the spinal cord. Studies included in my doctoral thesis investigate the possibilities of regulation of synaptic strength by cytokine TNFα, insulin and TRPV1 receptors agonist *N*-oleoyldopamine (OLDA). These three compounds are synthesized in the CNS, while TNFα is produced in the spinal cord notably during neuropathy. TNFα and insulin have a potential to modulate synaptic transmission. Endogenous TRPV1 receptors agonist OLDA can activate spinal TRPV1 receptors, which are highly expressed on central endings of nociceptive dorsal root ganglion (DRG) neurons. TRPV1 receptors are known as integrators of nociceptive stimuli particularly from the studies of peripheral receptors on nociceptors, which could be sensitized by inflammatory mediators and activated by temperature increase or decrease pH that is unlike in the spinal cord.

In our experiments miniature excitatory postsynaptic currents (mEPSCs) or evoked EPSCs were recorded in superficial dorsal horn neurons in acute spinal cord slices using patch-clamp technique. Under control conditions a high 10 μM concentration of OLDA application was needed for TRPV1 receptors activation registered as increase in mEPSC frequency in spinal neurons. Sensitization of TRPV1 receptors by protein kinase C activator application, inflammatory mediator bradykinin pretreatment or slice incubation with cytokine TNFα significantly decreased the concentration of OLDA needed to activate the TRPV1 receptors (0.2 μM). Importantly, similar increase in TRPV1 receptors sensitivity to endogenous agonist OLDA was present in model of experimentally induced peripheral inflammation. Increased sensitivity of spinal TRPV1 receptors to endogenous agonists may considerably modulate nociceptive synaptic transmission. Additional experiments showed that insulin induced depression of AMPA EPSCs, dependent on protein tyrosine kinase, probably due to AMPA receptors internalization. This suggests a new role for insulin in modulation of nociceptive signaling. Elucidation of presynaptic and postsynaptic mechanisms of synaptic transmission modulation at spinal cord level, namely under pathological conditions, is important for development of new generation of analgesics.