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Mechanisms of heat-gated nociception in primary and dorsal horn sensory neurons of the rat

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Noxious heat is a natural stimulus that activates peripheral sensory neurons expressing heat-gated ion channels. Recently, the TRPM3 channel emerged as a noxious heat sensor independent of TRPV1, which is also sensitive to the neurosteroid Pregnenolone sulphate (PS). Recently, evidence of a direct mechanism that controls the agonist-induced TRPM3 channel activity by activation of the μ-opioid receptor (MOR) has been described, through direct binding of the G-beta-gamma subunit to TRPM3.
The submitted thesis investigated mechanisms of heat-induced nociception using near-infrared laser stimulation as a rapid and accurate way to apply noxious heat. Responses to laser-heat were analyzed: in vitro by functional assays on heterologous expression systems and primary culture of sensory neurons, and in vivo by behavioral experiments and electrophysiological recordings at the dorsal horn of the spinal cord.
Laser-heat activates TRPV1 and TRPM3 channels in heterologous expression systems with activation thresholds of about 574 μJ and 615 μJ. The response amplitudes of TRPM3 upon activation with PS exceeded those of maximum laser stimulation (1.5 ± 0.003 of the ratio 340/380 versus 0.66 ± 0.011). Chemical- and thermal- induced activity of the TRPM3 channel co-expressing the MOR was reduced with DAMGO by 63.4% and 44.5%. In DRGs, 15-25% of all neurons analyzed (n= 550) functionally co-expressed TRPV1 and TRPM3, 38% expressed TRPV1 independent of TRPM3, 7-8% expressed TRPM3 but not TRPV1. DRG neurons displayed a direct inhibition by 18 ± 4.1% and 23 ± 3% when co-applying the MOR agonist DAMGO with PS. In the dorsal horn of the spinal cord, the processing of peripheral laser stimulation was carried out by a subset of WDR and HTM neurons, which were found at all depths of the dorsal horn (range: 120-820 μm). Laser-heat stimuli induced pain-behavior in vivo. All neurons that responded to suprathreshold laser-heat were nociceptive, including one third of WDR neurons and half of HTM neurons investigated. No laser-heat responses of LTM neurons were found. The peripheral input of the laser sensitive neurons was composed of C- and A- fibers; however, responses to laser-heat were transmitted by C-fibers. The sizes of the heat receptive fields ranged 10% - 60% of the mechanical receptive field and they located always inside them. The number of AP following laser stimulation was higher in HTM neurons compared to WDR neurons (14 ± 0.7 vs 9 ± 4.3), however not significant, and the latencies after onset of the laser stimulation were 266 ± 16 ms and 308.3 ± 55. The estimated temperature threshold for laser sensitive WDR neurons and HTM neurons (40.1 °C and 43.3 °C) was comparable to the mean heat withdrawal threshold in awake rats (41 °C). Differences in the proportions of neurons expressing TRPM3 and/or TRPV1 could be responsible for those differences in receptive field sizes. Since the threshold for laser-heat activation of the TRPM3 channel was higher than the threshold for TRPV1, a greater proportion of peripheral neurons containing TRPM3 might converge in dorsal horn laser sensitive HTM neurons than for laser sensitive WDR neurons.