WTH13 Sensory Systems

WTH13-01

Function of presynaptic TRPV1 receptors in the spinal cord dorsal horn is modulated by chemotherapeutic drug paclitaxel

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Neuropathic pain is major treatment-limiting factor accompanying cancer treatment with paclitaxel (PAC). We have reported previously (Li *et al.*, J. Neurosci., 35:13487–13500, 2015) that acute application of PAC (50 nM) modulated miniature excitatory postsynaptic currents (mEPSC) frequency and diminished tachyphylaxis of TRPV1 (transient receptor potential vanilloid 1) receptors mediated response after repeated capsaicin application via TLR4 receptors activation. Here we studied the signaling pathways involved in PAC-induced modulation. Whole-cell patch clamp recordings of mEPSC from spinal cord neurons in lamina I/II from adult male mice were used. Von Frey filament measurements were used to evaluate the presence of mechanical allodynia. PAC-neuropathy was induced by single dose application of PAC (8 mg/kg, *i.p.*). In naïve animals mEPSCs frequency evoked by second capsaicin application was reduced to 33% of the first one. After acute PAC-treatment the second response was 91% of the first one. Our data show that the second capsaicin response tachyphylaxis was diminished also 1 day (72%) and 8 days (83%) after single systemic *in-vivo* PAC-treatment. Effect of PAC treatment on tachyphylaxis was significantly reduced by PI3-Kinase antagonist wortmannin or LY294002 and by wide-spectrum kinases inhibitor staurosporine. These results suggest that PI3-Kinase and other kinases may play important role in the signaling between TLR4 and TRPV1 receptors in the spinal cord dorsal horn and may be involved in the development of painful states after PAC treatment. Targeting these molecules may represent a possible option for analgesic treatment in states of paclitaxel induced neuropathic pain. Our work was supported by grant support: GAUK 138215, LQ1604 BIOCEV-FAR, GACR 15-11138S, LH15279, GACR P304/12/G069, CZ.1.05/1.1.00/02.0109, RVO67985823.

WTH13-02

Peptidergic modulation of pain and anxiety: forebrain relaxin-3/RXFP3 networks and descending control of nociception in mice

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Persistent pain can hinder normal function and behaviour, with a negative impact on quality-of-life. In persistent pain conditions, patients develop conditions such as anxiety, which worsens pain sensation, creating a feedback loop between pain and this comorbid state. Anxiety is linked to altered function in brain areas innervated by relaxin-3 neurons. Indeed, activation of its receptor, Relaxin/Insulin Family Peptide Receptor 3 (RXFP3), can alter arousal, stress- and anxiety-related and reward-seeking behaviours in rodents. These data suggest a possible link between RXFP3 activity and control of pain sensitivity. Thus, these studies assessed the effect of RXFP3 activation/inhibition on the control of mechanical and thermal pain sensitivity in normal and persistent pain conditions in mice. Intracerebroventricular (icv) administration of RXFP3 agonist peptide reduced mechanical, but not thermal, pain sensation in C57BL/6J mouse model of inflammatory pain ($n = 5$ mice/group, $p < 0.01$). These effects were associated with decreased activity of nociceptive neurons in spinal cord ($n = 6$ mice, $p < 0.05$). In addition, RXFP3 antagonist augmented mechanical and thermal pain sensitivity ($n = 7$ mice/group, $p > 0.05$). These data suggest that relaxin-3 provides a tonic drive to maintain mechanical and thermal pain thresholds. In parallel, we sought to identify the neuronal circuits responsible for the observed effects. Using neural tract-tracing, we identified brain areas that receive relaxin-3 inputs, which in turn innervate the rostroventral medulla (RVM), a region that gates descending pain control. These regions include anterior cingulate cortex, central amygdala, bed nucleus of the stria terminalis and hypothalamus, which are functionally related to pain sensation and comorbidities. Together, these data suggest RXFP3 as a therapeutic target for pain management, and further studies of the specific circuits and mechanisms involved are warranted.

WTH13-03

Bifurcate spinal dorsal neurons projecting simultaneously to supraspinal centers by the dorsal column and the anterolateral system

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Sensory information arriving at the spinal dorsal horn (SDH) neurons can be transmitted to the supraspinal centers by two main systems: the dorsal column-medial lemniscal (DC-ML) or by the antero-lateral system (AL). These systems are well recognized and studied and the main conclusion is their independence or lack of interactions. To our knowledge no study has proposed their interactions as well as their bilateral projections. In order to test this hypothesis, we perform some neurochemical (retrograde neuronal tracing) and electrophysiological experiments in rats. We study principal SDH neurons at the L2-L5 segments having the characteristic of sending projections to the *Gracilis* nuclei (GRA) from the DC-ML or to the ventral postero lateral thalamic (VPL) nuclei from the AL. True Blue (TB) tracer was placed into the left GRA and Fluoro Gold (FG) or Fluor Rubi (FR) tracer was injected in the right VPL. After 13 days, the animals were perfused to localized the stained cells in spinal cord (SC). In order to test the functionality of the neurons founded we used concentric bipolar