Title: Activation of peripheral β2 and β3ARs leads to increased nociceptor activity

Authors: Xin Zhang, Seungtae Kim, Sandra C. O'Buckley, Harrison Ballard, Andrea G Nackley*

Abstract: Enhanced catecholamine tone resulting from decreased activity of catechol-Omethyltransferase (COMT; an enzyme that metabolizes catecholamines) contributes to functional pain syndromes, such as fibromyalgia and temporomandibular disorder. In line with findings from clinical studies, our lab has shown that acute delivery of a COMT inhibitor OR486 in rodents induces pronounced pain, which is mediated by β2- and β3ARs-dependent increases in nitric oxide and cytokines. However, the effects of COMT inhibition on nociceptor activity remain unknown. The present study sought to directly investigate the effects of COMT inhibition on dorsal root ganglion (DRG) nociceptor activity using immunohistochemistry in wild-type mice and in vivo calcium imaging in pirt-GCaMP3 mice (that express a calcium indicator exclusively in peripheral nociceptors). Separate groups of mice received systemic delivery of the COMT inhibitor OR486 or vehicle alongside peripheral delivery of the β2AR antagonist (ICI-118,551), β3AR antagonist (SR59230A) or vehicle. We determined that OR486-induced increases in pain sensitivity are accompanied by increases in ERK phosphorylation in DRG neurons and strengthened nociceptor activity in response to noxious stimuli in a β2- and β3ARsdependent manner. Collectively, these findings show that peripheral β2- and β3ARs drive the activity of nociceptors essential for the development of functional pain. Thus, treatments targeted towards peripheral βARs and downstream effectors may prove useful in the management of functional pain syndromes.

Funding: NIH/NINDS R01-NS072205 and P01-NS045685 to A.N.