Distribution of ecto-nucleotidases in mouse sensory circuits suggests roles for nucleoside triphosphate diphosphohydrolase-3 in nociception and mechanoreception 1H. Usman-Vongtau, E. Lavoie, J. Sévigny, D. Moliiver. 1Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA.

ABSTRACT Nucleotide-activated P2X channels and P2Y metabotropic receptors participate in nociceptive signaling. Agonist availability is regulated by nucleoside triphosphate diphosphohydrolase-1 (NTPDase1), -2, -3, and -8, a family of enzymes that hydrolyze extracellular ATP to generate ADP (a P2Y agonist) and AMP. They provide a major source of extracellular AMP, the substrate for adenosine production by ecto-5'-nucleotidase (NT5E), and thereby regulate adenosine (P1) receptor signaling. NTPDases vary in their efficiency of tri- and diphosphate hydrolysis; therefore, which family members are expressed impacts nucleotide availability and half-life. This study employed enzyme activity histochemistry to examine the distribution of ATPase activity and immunohistochemistry for NTPDase1, 2, 3, and 8 in dorsal root ganglion (DRG) and spinal cord. Nucleotidase activity was robust in spinal dorsal horn, confirming that nociceptive pathways are a major site of nucleotide transmission. In DRG, extensive staining revealed ATPase activity in a subset of neurons and in non-neuronal cells. mRNA for NTPDase1-3, but not NTPDase8, was detected in lumbar DRG and spinal cord.

Immunoreactivity for NTPDase3 closely matched the distribution of ATPase activity, labeling DRG central projections in the dorsal root and superficial dorsal horn, as well as intrinsic spinal neurons concentrated in lamina II. In DRG, NTPDase3 co-localized with markers of nociceptors and with NT5E. In addition, labeling of a subset of larger-diameter neurons in DRG was consistent with intense staining of Meissner corpuscle afferents in glabrous skin. Merkel cells and terminal Schwann cells of hair follicle afferents were also labeled, but the axons themselves were negative. We propose that NTPDase3 is a key regulator of nociceptive signaling that also makes an unexpected contribution to innocuous tactile sensation.