SHORT COMMUNICATION

ROLE OF TNAP AND OTHER ECTONUCLEOTIDASES IN PAIN MECHANISMS

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Prostatic acid phosphatase (PAP) and ecto-5'-nucleotidase (NT5E, CD73) produce extracellular adenosine from the nucleotide AMP in spinal nociceptive (pain-sensing) circuits; however, it is currently unknown if these are the main ectonucleotidases that generate adenosine or how rapidly they generate adenosine. We found that AMP hydrolysis, when measured histochemically, was nearly abolished in dorsal root ganglia (DRG) neurons and lamina II of spinal cord from Pap/Nt5e double knockout (dKO) mice. Likewise, the antinociceptive effects of AMP, when combined with nucleoside transport inhibitors (dipyridamole or 5-iodotubericidin), were reduced by 80-100% in dKO mice. In addition, we used fast scan cyclic voltammetry (FSCV) to measure adenosine production at subsecond resolution within lamina II. Adenosine was maximally produced within seconds from AMP in wild-type (WT) mice but production was reduced >50% in dKO mice, indicating PAP and NT5E rapidly generate adenosine in lamina II. Field potential recordings in lamina II and behavioral studies indicate that adenosine made by these enzymes acts through the adenosine A1 receptor to inhibit excitatory neurotransmission and nociception. Collectively, our experiments indicate that PAP and NT5E are the main ectonucleotidases that generate adenosine in nociceptive circuits transform pulsatile or sustained nucleotide release into an inhibitory adenosinergic signal. However, given that adenosine production was not eliminated in dKO mice, there likely exists at least one more ectonucleotidase in nociceptive circuits. Preliminary data to be presented suggests this third enzyme is tissuenonspecific alkaline phosphatase (TNAP).