address these issues and continue to elucidate the epigenetic mechanisms that generate long-term behavioral change.

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DISCLOSURE

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Emerging Roles for Ectonucleotidases in Pain-Sensing Neurons

Nociceptive neurons located in the dorsal root ganglia detect painful stimuli and can be sensitized following inflammation or nerve injury. Many analgesics have 'antinociceptive' effects, which mean these drugs can reduce noxious thermal and mechanical sensitization—two symptoms that are associated with chronic pain. One drug that has been studied for its antinociceptive effects in rodents and humans is adenosine (Sawynok and Liu, 2003). Adenosine exerts its antinociceptive effects by activating the adenosine A_1 receptor (A_1R). A_1R is expressed by nociceptive neurons and many other cells of the body, suggesting localized activation of this receptor in nociceptive neurons might inhibit pain without producing cardiovascular and other effects that are associated with systemic A_1R activation. Recently, several new studies found that A_1R can be activated locally near nociceptive neurons or their axons by ectonucleotidases—a class of enzymes that hydrolyze extracellular adenine nucleotides to adenosine. Moreover, this localized A_1R activation was sufficient to inhibit chronic pain in animal models.

In the first set of studies, our lab found that prostatic acid phosphatase (PAP) and ecto-5′-nucleotidase (NT5E, also known as CD73) function as ectonucleotidases in nociceptive neurons (Sowa *et al*, 2010a; Zylka *et al*, 2008). PAP and NT5E can each hydrolyze extracellular adenosine 5′-monophosphate (AMP) to adenosine. In histochemical assays, AMP hydrolysis was reduced (but not eliminated) in nociceptive neurons from PAP and NT5E knockout mice. PAP and NT5E knockout mice also showed enhanced nociception in models of inflammatory and neuropathic pain. These enhanced responses from genetically eliminating enzymes that make adenosine were similar to the enhanced nociception phenotypes observed by Wu and colleagues in mice lacking A_1R (Wu *et al*, 2005).

PAP and NT5E can each be purified as nonmembrane-bound enzymatically active proteins. This feature provided us with a means to transiently increase the amount of PAP or NT5E activity *in vivo*. Specifically, we found that intrathecal injection of soluble PAP or NT5E protein had dose-dependent and long-lasting antinociceptive effects in animal models of inflammatory pain and neuropathic pain (Sowa *et al*, 2010b; Zylka *et al*, 2008). The antinociceptive effects of PAP lasted for 3 days after a single intrathecal injection whereas the antinociceptive effects of NT5E lasted 2 days. The antinociceptive effects of both enzymes were dependent on A_1R activation, suggesting that PAP and NT5E act through their ability to generate adenosine from AMP. Moreover, these findings suggest ectonucleotidases could be developed as enzyme-based treatments for some forms of chronic pain.

In another recent study, Goldman *et al.* (2010) found that localized A_1R activation underlies the antinociceptive effects of acupuncture. Manual stimulation of acupuncture needles resulted in localized extracellular increases in nucleotides (ATP, ADP, and AMP) and adenosine. The ectonucleotidases responsible for generating adenosine were not identified in this study; however, indirect evidence suggests PAP may be a candidate. Collectively, these studies reveal roles for localized A_1R activation and ectonucleotidases in nociceptive neurons and offer new approaches for treating chronic pain.

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