probably fail in adolescents, a hypothesis supported by a study comparing adolescent and adult smokers (Smith *et al*, 2008). Our neurochemical data also suggest that adolescents may be less sensitive to current treatments that facilitate dopamine (such as Zyban), as they may not show deficits in dopamine during withdrawal. Given the strong rewarding effects of nicotine during adolescence, the best strategy for reducing tobacco abuse may be to strictly reduce access to nicotine-containing products during this developmental period. Furthermore, pharmacological treatments for adolescent smokers may target the strong rewarding effects of nicotine that appear to be mediated through mesolimbic dopamine and upstream glutamatergic mechanisms that modulate this reward pathway. Future work is needed to validate the role of these mechanisms in adolescent tobacco abuse, and to examine whether they also mediate long-term vulnerability to tobacco abuse in adults that initiated smoking during adolescence.

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DISCLOSURE

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Mansvelder HD, McGehee DS (2002). Cellular and synaptic mechanisms of nicotine addiction. *J Neurobiol* **53**: 606–617.

McDonald JW, Johnston MV (1990). Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res Rev* **15**: 41–70.

Natividad LA, Tejeda HA, Torres OV, O'Dell LE (2010). Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. *Synapse* **64**: 136–145.

O'Dell LE (2009). A psychobiological framework of the substrates that mediate nicotine use during adolescence. *Neuropharmacology* **56**: 263–278.

Shearman E, Fallon S, Sershen H, Lajtha A (2008). Nicotine-induced monoamine neurotransmitter changes in the brain of young rats. *Brain Res Bull* **76**: 626–639.

Smith AE, Cavallo DA, Dahl T, Wu R, George TP, Krishnan-Sarin S (2008). Effects of acute tobacco abstinence in adolescent smokers as compared with nonsmokers. *J Adol Health* **43**: 46–54.

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Epigenetic Modifications in Neurons are Essential for Formation and Storage of Behavioral Memory

Understanding the molecular mechanisms that produce and maintain long-lasting changes in brain function is critical for numerous areas of neuroscience research, and is especially relevant in the context of learning and memory. Increasing evidence now indicates that epigenetic modifications in neurons may be essential mechanisms for both the formation and storage of behavioral memory. For example, the formation and recall of contextual fear memories increases histone tagging (acetylation) in the hippocampus (Levenson *et al*., 2004). Blocking histone acetylation impairs both long lasting synaptic plasticity as well as behavioral performance (Korzus *et al*., 2004). Similarly, inhibition of histone deacetylase (HDAC) activity rescues these deficits and improves memory formation (Korzus *et al*., 2004; Levenson *et al*., 2004). Finally, normal aging-related memory impairment is associated with the lack of a specific histone acetylation mark, which can be rescued by treatment with an HDAC inhibitor to restore memory function (Peleg *et al*., 2010).

DNA methylation, a second form of epigenetic marking, also has a critical role in memory formation and consolidation. Contextual fear conditioning induces rapid methylation of a memory suppression gene (*protein phosphatase 1*, *PP1*) and demethylation of plasticity genes (*reelin* and *brain-derived neurotrophic factor*, *BDNF*) in the hippocampus (Lubin and Sweatt, 2007; Miller and Sweatt, 2007). Moreover, inhibition of DNA methyltranferases, which are required for DNA methylation, prevents memory formation (Lubin and Sweatt, 2007; Miller and Sweatt, 2007). Interestingly, both histone and DNA methylation changes that occur in the hippocampus after learning are relatively transient compared with the lifetime of a memory, indicating that other mechanisms are involved in long-term memory storage. However, a recent study found that learning can induce long-lasting DNA methylation changes in the anterior cingulate cortex, and that these changes are essential for the recall of remote memories for up to a month after conditioning (Miller *et al*., 2010). This finding is particularly exciting because it (1) reveals a molecular change that lasts long enough to subserve the maintenance of long-term memory, and (2) indicates region-specific regulation of DNA methylation that is largely in line with the functional roles of the hippocampus and cortex in memory consolidation and storage, respectively.

Taken together, these findings indicate that epigenetic mechanisms are key regulators of long-term memory and reveal several potential therapeutic targets for the amelioration of memory-related diseases. Nevertheless, a number of important questions remain to be answered. For example, it is unclear whether diverse histone marks and DNA methylation profiles operate in relative isolation or are integrated as part of an 'epigenetic code' to generate meaningful changes in gene expression and behavior. In addition, it is unclear how cell-wide changes associated with epigenetic modifications interact with synapse-specific changes long believed to underlie learning and memory processes. Finally, it is uncertain how specific epigenetic modifications are targeted within a cell and how the kinetics underlying such modifications may differ between brain regions to confer circuit-specific epigenetic patterns. Future studies will be required to

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

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Korzus E, Rosenfeld MG, Mayford M (2004). CBP histone acetyltransferase activity is a critical component of memory consolidation. *Neuron* **42**: 961–972.

Levenson JM, O'Riordan KJ, Brown KD, Trinh MA, Molfese DL, Sweatt JD (2004). Regulation of histone acetylation during memory formation in the hippocampus. *J Biol Chem* **279**: 40545–40559.

Lubin FD, Sweatt JD (2007). The IkappaB kinase regulates chromatin structure during reconsolidation of conditioned fear memories. *Neuron* **55**: 942–957.

Miller CA, Sweatt JD (2007). Covalent modification of DNA regulates memory formation. *Neuron* **53**: 857–869.

Miller CA, Gavin CF, White JA, Parrish RR, Honasoge A, Yancey CR *et al* (2010). Cortical DNA methylation maintains remote memory. *Nat Neurosci* **13**: 664–666.

Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, Agis-Balboa RC *et al.* (2010). Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science* **328**: 753–756.

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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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The authors declare no conflict of interest.

Goldman N, Chen M, Fujita T, Xu Q, Peng W, Liu W *et al* (2010). Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture. *Nat Neurosci* **13**: 883–888.

Sawynok J, Liu XJ (2003). Adenosine in the spinal cord and periphery: release and regulation of pain. *Prog Neurobiol* **69**: 313–340.

Sowa NA, Taylor-Blake B, Zylka MJ (2010a). Ecto-5′-nucleotidase (CD73) inhibits nociception by hydrolyzing AMP to adenosine in nociceptive circuits. *J Neurosci* **30**: 2235–2244.

Sowa NA, Voss MK, Zylka MJ (2010b). Recombinant ecto-5′-nucleotidase (CD73) has long lasting antinociceptive effects that are dependent on adenosine A1 receptor activation. *Mol Pain* **6**: 20.

Wu WA, Hao JX, Halldner L, Lovdahl C, DeLander GE, Wiesenfeld-Hallin Z *et al* (2005). Increased nociceptive responses in mice lacking the A1 receptor. *Pain* **113**: 395–404.

Zylka MJ, Sowa NA, Taylor-Blake B, Twomey MA, Herrala A, Voikar V *et al* (2008). Prostatic acid phosphatase is an ectonucleotidase and suppresses pain by generating adenosine. *Neuron* **60**: 111–122.

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