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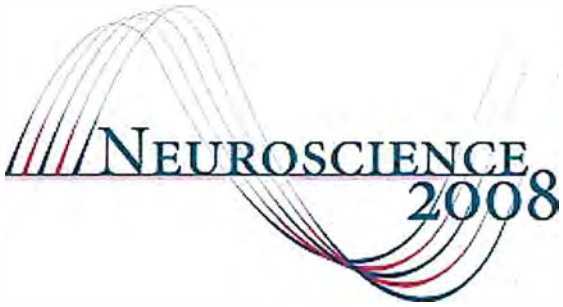

Presentation Abstract

Program#/Poster#: 727.6/D22

Title: Distinct roles of PDE4 and PDE10A in the regulation of cAMP/PKA signaling in the striatum

Location: Washington Convention Center: Hall A-C

Presentation Time: Wednesday, Nov 19, 2008, 9:00 AM -10:00 AM

Authors: ***A. NISHI**[1], M. KUROIWA[1], D. B. MILLER[2], J. P. O'CALLAGHAN[2], H. S. BATEUP[3], P. GREENGARD[3], G. L. SNYDER[4];
[1]Dept of Pharmacol, Kurume Univ. Sch. of Med., Kurume, Japan; [2]Centers for Dis. Control and Prevention, Natl. Inst. for Occup. Safety and Hlth., Morgantown, WV; [3]Lab. of Mol and Cell Neurosci, The Rockefeller Univ., New York, NY; [4]Intra-Cellular Therapies, Inc., New York, NY

Abstract: Phosphodiesterase (PDE) is a critical regulator of cAMP/PKA signaling in cells. Multiple PDEs with different substrate specificity and subcellular localization are expressed in neurons. Dopamine plays a central role in the regulation of motor and cognitive functions. The effect of dopamine is largely mediated through the cAMP/PKA signaling cascade, and therefore controlled by PDE activity. We used in vitro and in vivo biochemical techniques to dissect the role of PDE4 and PDE10A in dopaminergic neurotransmission in mouse striatum by monitoring the ability of selective PDE inhibitors to regulate phosphorylation of presynaptic (e.g., tyrosine hydroxylase or TH) and postsynaptic (e.g., DARPP-32) PKA substrates. The PDE4 inhibitor, rolipram, induced a large increase in TH Ser40 phosphorylation at dopaminergic terminals that was associated with a commensurate increase in dopamine synthesis and turnover in the striatum in vivo. Rolipram induced a small increase in DARPP-32 Thr34 phosphorylation preferentially in striatopallidal neurons by activating adenosine A2a receptor signaling in the striatum. In contrast, the PDE10A inhibitor, papaverine, had no effect on TH phosphorylation or dopamine turnover, but instead robustly increased DARPP-32 Thr34 and GluR1 Ser845 phosphorylation in striatal neurons.

Inhibition of PDE10A by papaverine activated cAMP/PKA signaling in both striatonigral and striatopallidal neurons, resulting in potentiation of dopamine D1 receptor signaling and inhibition of dopamine D2 receptor signaling. These biochemical results are supported by immunohistochemical data demonstrating differential localization of PDE10A and PDE4 in the striatum. These data underscore the importance of brain-enriched cyclic-nucleotide PDEs as therapeutic targets for neuropsychiatric and neurodegenerative disorders affecting dopamine neurotransmission.

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