Abstract:

EFFECTS OF A PDE10A INHIBITOR AND PDE10A2 DEFICIENCY ON VOLUNTARY ALCOHOL INTAKE IN MICE

L. B. Bertotto[1], S. Ranjan[1, 2], A. G. Ghoogasian [1, 3], G. Macedo[1], A. E. Pimentel[1], C. Cates-Gatto[4], A.J. Roberts[4] and E. P. Zorrilla[1]

[1]Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA 92037, USA
[2]Division of Biological Sciences, University of California, San Diego
[3]Department of Human Developmental Sciences, University of California, San Diego
[4]Animal Models Core Facility, The Scripps Research Institute, La Jolla, CA 92037, USA

Alcohol use disorder (AUD) is a chronic, relapsing disorder that afflicts 29% of Americans in their lifetime, can be disabling and increases mortality. New drug targets and neurobiological insight for AUD are needed. Excess drinking putatively involves a relative underactivity of indirect pathway medium spiny neurons (iMSNs) that subserve adaptive behavioral selection vs. overactive direct pathway MSNs (dMSNs) that drive drinking behaviors. Alcohol use increases availability of phosphodiesterase 10A (PDE10A), an enzyme localized in striatal MSNs that inactivates cAMP/cGMP, implicating a possible role in promoting further intake. Previously, we showed that PDE10A inhibitors reduced alcohol self-administration in rat models of excess and post-dependent drinking. Here, we hypothesized that decreasing the activity of PDE10A would reduce voluntary drinking in mice. To test our hypothesis, C57BL/6J mice (N=10/sex) received 2-bottle choice (2BC), 2-hr EtOH (20% *v/v*) and water access for 3 weeks and then were pretreated (-1 hr) with the selective PDE10A inhibitor AMG579 (i.p., 0 (10% HPßC), 55.5, 111, 222, 444 nmol/kg) in a within-subject design. Separately, we studied whether mice with heterozygote (+/-; *n*=32) or homozygote (-/-; *n*=29) genetic deletion of the striatal-restricted PDE10A2 isoform also showed reduced 2BC voluntary ethanol intake in the above paradigm vs. wildtype (+/+) controls (*n*=11). Systemic AMG579 significantly reduced EtOH intake, most effectively at the 111 nmol/kg dose (*M*+SEM: 2.71+0.45 vs. 1.57+0.35 g/kg, $p<0.05$). Female, but not male, PDE10A2$^{+/-}$ and PDE10A2$^{-/-}$ mice both showed reduced EtOH intake (1.83+0.24 and 1.72+0.25 g/kg) as compared to wildtype controls (3.53+0.35 g/kg). Collectively, the results support the hypothesis that striatal PDE10A modulates voluntary ethanol intake, perhaps differentially in females, and suggest potential impact of translatable PDE10A inhibitors to treat alcohol misuse.

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