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PHOSPHODIESTERASE TYPE 7: A NOVEL TARGET FOR SMOKING CESSATION -PRECLINICAL EVIDENCE-
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The nucleotide phosphodiesterase (PDE) type 7 family includes two members, PDE7A and PDE7B, which are cyclic-AMP-specific PDEs expressed in brain dopaminergic regions linked to addiction, such as the nucleus accumbens (NAc) and ventral tegmental area (VTA). Here we assessed the role of PDE7 in addiction by evaluating selective PDE7 inhibitors (PDE7i) OMS182399 and OMS182401 in rat models of nicotine self-administration and relapse to drug seeking. Our results showed that PDE7 inhibition by OMS182399 or OMS182401 significantly reduced fixed-ratio 3 (FR-3) and progressive ratio (PR) nicotine self-administration. In preclinical model of relapse we found that OMS182399 and OMS182401 also attenuated cue- and yohimbine-induced reinstatement of nicotine seeking. Food self-administration was not modified either drug. In rats implanted bilaterally with intracranial cannulas aimed at the VTA, we found that site specific injection of OMS182399 or OMS182401 into this brain area significantly reduced nicotine self-administration under both FR-3 and PR schedule of reinforcement suggesting a role of corticomeso-limbic dopaminergic circuitries in PDE7i effects. Biochemical analysis in different brain areas has been conducted to shed light on the mechanism of action of PDE7i. These findings suggest that PDE7 could be a novel therapeutic target for nicotine addiction.