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Effect of partial nicotinic agonists on real-time dopamine responses in rat nucleus accumbens: In vivo voltammetric study

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There is strong evidence that neuronal nicotinic receptors (NNRs) play a crucial role in the regulation of mesolimbic dopamine (DA) neurons but the exact receptor subtypes and mechanisms underlying their involvement are not understood. Elucidation of the role of receptor subtypes (e.g., α4-, α6- or α7-containing) in the ventral tegmental area (VTA) or nucleus accumbens (NAc) and their pharmacological properties (e.g., partial or full activation, inhibition, or desensitization) offers new insights for development of NNR-targeted therapies for smoking cessation and other conditions. Recent voltammetric studies on nicotinic activity at DA terminals in the striatum significantly contributed to the field but were limited by the properties of slice preparations or the use of nicotine ± antagonist approaches. The present work focused on the effects of nicotine and nicotinic partial agonists on accumbal DA release using fast-scan cyclic voltammetry *in vivo*. We used partial agonists (PAs) which in our previous studies exhibited medium efficacy and high potency (PA-A) or low efficacy and low potency (PA-B) relative to nicotine when measuring NNR-mediated [^{3}H]DA release from rat striatal synaptosomes. In the present study, nicotine (0.3 mg/kg, i.v.) induced marked DA efflux in the NAc of freely-moving and anesthetized rats. A 30-min pre-administration of PA-A (0.1 mg/kg and 0.3 mg/kg, i.p.) significantly diminished nicotine-evoked DA release in rat NAc. In addition, PA-A and PA-B (3 mg/kg, i.p.) and nicotine (0.3 mg/kg, i.v.) decreased the DA efflux elicited by electrical stimulation of the VTA (24 rectangular pulses, 60 Hz, 300 μA, 2 ms/phase) without affecting DA uptake. Importantly, both PA-A and PA-B attenuated nicotine-evoked DA responses in the NAc at doses that decreased nicotine self-administration in rats. Our study suggests the utility of *in vivo* voltammetry for translational studies of NNR-targeted drug candidates.

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An mGlu2/3 receptor agonist blocks increases in nucleus accumbens shell dopamine induced by self-administered, but not experimenter-administered, nicotine in rats

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Metabotropic glutamate (mGlu) 2/3 receptors that negatively regulate glutamatergic transmission are critically involved in the reinforcing effects of drugs of abuse, including nicotine. mGlu2/3 receptor agonist, LY379268 (1 mg/kg), has previously been shown to decrease nicotine self-administration and cue-induced nicotine-seeking behavior in rats. In addition, chronic nicotine self-administration resulted in downregulation of mGlu2/3 receptor function in mesocorticolimbic brain areas. We hypothesize here that LY379268 decreased the reinforcing effects of nicotine by attenuating nicotine-induced increase in NAcc dopamine. Using *in vivo* microdialysis, the present study examined the effect of systemic LY379268 (1 mg/kg, s.c.) pretreatment on nicotine-induced increase in NAcc shell dopamine and its metabolites (DOPAC, HVA and 5HIAA) in rats with a history of nicotine self-administration. Nicotine was administered either through an experimenter-administered subcutaneous injection (0.4 mg/kg, base) or through a single self-infusion of nicotine (0.06 mg/kg, base). Systemic LY379268 (1 mg/kg) pretreatment abolished NAcc shell dopamine increase after nicotine self-administration in nicotine-experienced rats. However, pretreatment with LY379268 (1 mg/kg) had no effect on the experimenter-administered nicotine-induced increase in dopamine in the NAcc shell in nicotine-experienced rats. Furthermore, LY379268 pretreatment did not influence the increase in dopamine metabolites after either self-administration of nicotine or experimenter-administered nicotine. These data indicate that the mGlu2/3 receptor agonist LY379268 plays an important role in blocking the combined effect of both nicotine and stimuli associated with nicotine self-administration. Further, based on these data we hypothesize that mGlu2/3 receptors play a more critical role in regulating the dopamine response to nicotine in the presence of stimuli associated with nicotine as compared to nicotine alone.

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$GABA_B$ receptor positive modulators: Effects on nicotine self-administration and cue-induced reinstatement of nicotine-seeking behavior in rats

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γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and is implicated in the modulation of central reward processes. Acute administration of γ-aminobutyric acid B ($GABA_B$) receptor agonists or positive modulators decreased self-administration of various drugs of abuse, such as nicotine, cocaine, ethanol and heroin, and inhibited cue-induced reinstatement of nicotine- and cocaine-seeking behavior. $GABA_B$ receptor positive modulators may be potentially improved therapeutic compounds for the treatment of drug dependence than $GABA_B$ receptor agonists due to fewer adverse side-effects. BHF177, a newly synthesized $GABA_B$ receptor positive modulator, decreased nicotine self-administration under a fixed-ratio 5 (FR5) and a progressive-ratio (PR) schedule of reinforcement in Wistar rats, while it did not affect food-maintained responding [1]. The present study investigated the effects of administration of another newly synthesized $GABA_B$ receptor positive modulator, BIK998, on nicotine- and food-maintained responding under a FR5 and a PR schedule of reinforcement. It also investigated the effects of BHF177 on cue-induced reinstatement of nicotine- and food-seeking behavior. Administration of BIK998 (0, 20, 40, 80 mg/kg, PO) did not affect nicotine self-administration, neither in the FR5 nor the PR schedule of reinforcement in either nicotine- or food-responding groups. The lack of effects seen with BIK998 may be attributed to sub-