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Targeting Nicotinic Receptor Antagonists as Novel Pharmacotherapies for Tobacco Dependence and Relapse

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Tobacco dependence is a significant health concern and the most preventable cause of death in the USA. Nicotine, the principal tobacco alkaloid, activates nicotinic receptors (nAChRs) on dopamine terminals in the mesolimbic and nigrostriatal systems to evoke dopamine release, leading to reward and tobacco dependence. Bupropion, which inhibits both neurotransmitter transporters and acts as a nAChR antagonist, has benefit as a smoking cessation agent. Also, mecamylamine, a noncompetitive antagonist at both central and peripheral nAChRs, has shown benefit in clinical trials, but is limited by anticholinergic side-effects due its lack of nAChR selectivity. Buproprion and mecamylamine provide proof of concept that nAChR antagonists have efficacy in treating nicotine addiction; however, high relapse rates indicate a continuing need for alternative pharmacotherapies.

Our hypothesis is that discovery of selective antagonists targeted at neuronal nAChRs mediating nicotine-evoked neurotransmitter release, which mediates the reinforcing effects of nicotine, will provide clinically-effective smoking cessation agents, circumventing unwanted side-effects. The current pharmacological approach using a subtype-selective nAChR antagonist to reversibly block the specific nAChR subtype mediating the reinforcing effects of nicotine is similar to employing nAChR subunit deletion to prevent the expression of these nAChRs. In this regard, landmark work has shown that in beta2 subunit knockout mice, targeted injection into the ventral tegmental area of a lentiviral vector which efficiently expresses beta2 subunit protein restores both nicotine-evoked dopamine release in the nucleus accumbens and nicotine reinforcement, providing convincing evidence that beta2 containing nAChRs expressed specifically in the ventral tegmental area play a major role in the reinforcing effects of nicotine (Molles et al., 2006).

Because nicotine interacts with all nAChR subtypes, discovery of subtype-selective nAChR antagonists that inhibit nicotine-evoked dopamine release was initiated using nicotine as the structural scaffold. Simple addition of an *N*-*n*-alkyl group converted nicotine from an agonist to an antagonist, and subtype selectivity began to emerge depending on the number of methylene groups in the *n*-alkyl chain (Dwoskin et al., 2004). The classic discovery that the *bis*-tri-alkylammonium nAChR channel blockers, hexamethonium and decamethonium, exhibit subtype-selectivity between ganglionic and muscle-type nAChRs led us to employ a similar approach by generating a sub-library of small molecules consisting of a *bis*-nicotinium analog structure, incorporating a variety of head groups and diverse linkers varying in length, unsaturation and polarity. From this novel sub-library, a new lead compound, *N*,*N*'-dodecyl-1,12-diyl-*bis*-3-picolinium dibromide (bPiDDB), emerged. bPiDDB potently inhibited nicotine-evoked dopamine release from superfused rat striatal slices (Dwoskin et al., 2008a). Using microdialysis, systemically-administered bPiDDB also inhibited the nicotine-induced increase in extracellular dopamine in nucleus accumbens (Rahman et al., 2007). Thus, following *in vitro* and *in vivo* peripheral administration, bPiDDB decreased nicotine-evoked dopamine release. Utilizing radiolabelled-bPiDDB, we also demonstrated its brain bioavailability via the blood-brain barrier choline transporter (Albayati et al., 2008)

Investigation of the behavioral pharmacology of bPiDDB revealed that this compound decreases nicotine-induced hyperactivity in nicotine-sensitized rats, a response associated previously with enhanced nicotine-evoked dopamine release in nucleus accumbens. Since bPiDDB did not reduce activity when administered alone in nicotine-sensitized rats, the decrease in nicotine-induced hyperactivity is not due to nonspecific motor impairment, but rather likely reflects inhibition of nicotine-evoked dopamine release. Moreover, bPiDDB decreases intravenous nicotine self-administration in rats (Neugebauer et al., 2006). Surprisingly, bPiDDB did not block the discriminative stimulus effects of nicotine, indicating that bPiDDB dissociates the rewarding and discriminative stimulus properties of nicotine (Dwoskin et al., 2008a). Following extinction of nicotine self-administration, bPiDDB also attenuated nicotine-induced reinstatement of nicotine seeking behavior in rats (Dwoskin et al., 2008b). Taken together, the effectiveness of bPiDDB in decreasing both nicotine self-administration and reinstatement designates bPiDDB as a lead in our search for nAChR antagonists that may be a useful as treatments for tobacco dependence and relapse.

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