New Product Highlights

ABT 418: A novel neuronal nicotinic acetylcholine receptor agonist with cognition enhancing and anxiolytic activities

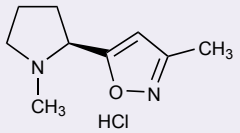
Nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated cation channels that are activated by the alkaloid **(–)-nicotine** (Prod. No. N 3876) and are classified on the basis of their subunit structure [1]. These non-selective conductance channels for calcium, potassium and sodium ions are pentameric in structure and are formed from a diverse range of subunits. Ten α (α1-α10) and four β (β1-β4) subunits have been cloned from mammalian and avian sources. Additional γ, δ and ε subunits are associated with nAChRs present at the neuromuscular junction [1-3]. Homo- and heteromeric combinations of these various subunits offer considerable potential for both structural and functional diversity.

Until recently, few selective ligands have been widely available with which to study nAChRs. Such compounds include the sedative α4β2 antagonist **dihydro-β-erythroidine** (Prod. No. D-149) and the selective α7 antagonists **methyllycaconitine** (Prod. No. M-168) and **MG-264** (Prod. No. M 3184). Sigma-RBI is therefore pleased to introduce **ABT 418** (Prod. No. A 6476), a novel bioisostere of (–)-nicotine that is a full agonist at the α4β2 neuronal nAChR which is a predominant form of nAChR in the central nervous system (CNS).

ABT 418 is a potent displacer of [^{3}H]-cytisine binding to rat brain nAChRs (K_i = 3 nM) while being essentially inactive (K_i > 10 μM) in a wide range of other receptor/neurotransmitter uptake/enzyme assays, including those for muscarinic and 5-HT_3 serotonin receptors [3]. Moreover, as compared with (–)-nicotine, ABT 418 demonstrated a reduced potency at the subunit isoforms of nAChR found in sympathetic ganglia. In rodent behavioral tests, ABT 418 improved retention of inhibitory avoidance training, demonstrated anxiolytic-like effects as measured in the elevated plus maze and enhanced basal forebrain stimulation-induced cortical cerebral blood flow [5,6]. In inducing the above effects, ABT 418 was at least as potent as (–)-nicotine while being significantly less potent than (–)-nicotine at producing a number of undesirable side effects, notably emesis, hypothermia and seizures.

Of particular interest from a clinical standpoint was the observation that ABT 418 stimulated the release of dopamine from rat striatal slices, albeit with a 10-fold lower potency as compared to (–)-nicotine [4]. In a small clinical trial in Alzheimer's disease patients, subjects receiving ABT 418 acutely showed significant improvements in total recall and a decline in recall failure on a verbal learning task [7]. The compound was subsequently shown to possess efficacy in a limited attention-deficit hyperactivity disorder (ADHD) trial in adults [8], a behavioral disorder characterized by distractibility and impulsiveness that is currently treated by a range of drugs that are believed to augment dopaminergic neurotransmission.

Given its high selectivity for the neuronal α4β2 nAChR, its robust efficacy in several animal behavioral models and its observed clinical effects, ABT 418 should prove to be a major new research tool with which to further investigate the contribution of neuronal α4β2 nAChRs to a range of centrally-mediated behaviors.



ABT 418
(Prod. No. A 6476)

Subject to U.S. Patent No. 5409946 and sold under license from Abbott Laboratories.

References

1. Lukas, R.J. et al., *Pharmacol. Rev.*, **51**, 397-401 (1999).
2. Lloyd, K.G. and Williams, M., *J. Pharmacol. Exp. Ther.*, **292**, 461-467 (2000).
3. Dani, J.A., *Biol. Psychiatry*, **49**, 166-174 (2001).
4. Arneric, S.P. et al., *J. Pharmacol. Exp. Ther.*, **270**, 310-318 (1994).
5. Decker, M.W. et al., *J. Pharmacol. Exp. Ther.*, **270**, 319-328 (1994).
6. Brioni, J.D. et al., *J. Pharmacol. Exp. Ther.*, **271**, 353-361 (1994).
7. Potter, A. et al., *Psychopharmacology*, **142**, 334-342 (1999).
8. Wilens, T.E. et al., *Am. J. Psychiatry*, **156**, 1931-1937 (1999).