BP 897, a Selective Dopamine D3 Receptor Ligand with Therapeutic Potential for the Treatment of Cocaine-Addiction

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Key words: BP 897—Cocaine—Craving—D3 receptors—Drug abuse—Withdrawal.

ABSTRACT

BP 897 is a potent ($K_i = 0.92$ nM) dopamine D3 receptor compound developed for the treatment of cocaine abuse and craving. BP 897 has a high selectivity for the dopamine D3 versus D2 receptors (70-fold) and a moderate affinity for 5-HT1A receptors, ($K_i = 84$ nM), adrenergic-$\alpha_1$ ($K_i = 60$ nM) and -$\alpha_2$ adrenoceptors ($K_i = 83$ nM). BP 897 displays significant intrinsic activity at the human dopamine D3 receptor by decreasing forskolin-stimulated cAMP levels and by stimulating mitogenesis of dopamine D3-expressing NG108-15 cells. Although these findings suggest that BP 897 is a partial agonist, recent studies in Chinese Hamster Ovary (CHO) cells with expressed dopamine D3 receptors demonstrated that BP 897 is devoid of any intrinsic activity but potently inhibits dopamine agonist effects (pIC50 = 9.43 and 9.51) in agonist-induced acidification rate or increase of GTPγS binding, respectively. In addition, BP 897 inhibits in vivo (EC50 = 1.1 mg/kg, i.v.) agonist-induced decrease of firing rate of dopaminergic neurons in the substantia nigra.

It has been clearly shown that BP 897, 1 mg/kg, i.p., reduces cocaine-seeking behavior in rats, without producing reinforcement on its own. In rhesus monkeys, BP 897 is not self-administered (up to 30 $\mu$g/kg, i.v.) but reduces cocaine self-administration. The potential usefulness of BP 897 in the treatment of drug-seeking behavior is further supported by its effects in drug conditioning models. Although BP 897 reduces L-DOPA–induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys, it provokes a return of parkinsonian symptoms. At high doses BP 897 has been reported to produce catalepsy in rats. Pharmacokinetic and toxicological data have not yet been published. These interesting preclinical findings with BP 897 provide additional validation for dopamine D3 receptor as a therapeutic target for the treatment of cocaine abuse and its associated central nervous system (CNS) disorders. BP 897 recently entered phase II clinical studies.