ABT-089: Pharmacological Properties of a Neuronal Nicotinic Acetylcholine Receptor Agonist for the Potential Treatment of Cognitive Disorders


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ABSTRACT

ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride salt] is a selective neuronal nicotinic receptor (NNR) modulator with cognitive enhancing properties in animal models of cognitive functioning. Amongst NNR subtypes, ABT-089 shows selectivity for the cytisine binding site on the \( \alpha_4\beta_2 \) receptor subtype as compared to the \( \alpha\)-bungarotoxin (\( \alpha\)-BgT) binding sites on the \( \alpha_7 \) and \( \alpha_4\beta_1\delta \) receptor subtypes. In functional in vitro electrophysiological and cation flux assays, ABT-089 displays differential activity including agonism, partial agonism and antagonism depending upon the NNR subtype and assay. ABT-089 is as potent and efficacious as \((-\)-)nicotine at evoking acetylcholine (ACh) release from hippocampal synaptosomes. Furthermore, ABT-089 is neuroprotective against excitotoxic glutamate insults, with even greater potency seen after chronic treatment. Similarly, ABT-089 is effective in models of cognitive functioning, including enhancement of baseline functioning as well as improvement of impaired cognitive functioning seen following septal lesioning and natural aging. In neuroprotective assays the compound is most potent by chronic administration. In stark contrast to the positive effects in the cognitive models, ABT-089 shows little propensity to induce adverse
effects such as ataxia, hypothermia, seizures, cardiovascular or gastrointestinal side effects. Together these data suggest that ABT-089 is a NNR modulator with the potential for treating cognitive disorders with markedly limited adverse cardiovascular and gastrointestinal side effects.