Cotinine, a Neuroactive Metabolite of Nicotine: Potential for Treating Disorders of Impaired Cognition

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ABSTRACT

The pharmacological effects of the tobacco-derived alkaloid nicotine have been widely studied in humans and animals for decades. However, relatively little attention has been given to the potential actions of its major metabolite, cotinine. After nicotine consumption the duration of cotinine’s presence in blood and brain greatly exceeds that of nicotine. Therefore, cotinine could mediate the more protracted pharmacological effects of nicotine. The studies described in this report were thus designed to further investigate certain neuropharmacological actions of cotinine. Behavioral tests (e.g., delayed matching-to-sample) were conducted in aged rhesus monkeys to assess the effects of cotinine on working memory and attention. In rats a prepulse inhibition (PPI) procedure was used to assess the effects of the compound on auditory gating — a method for predicting the potential antipsychotic properties of drugs. Cotinine exhibited significant effectiveness in these tasks. The drug was also cytoprotective in differentiated PC-12 cells with a potency equivalent to that of nicotine. The effects of chronic cotinine treatment on the expression of nicotinic and muscarinic acetylcholine receptors in rat brain were measured by [125I]epibatidine, [125I]α-bungarotoxin ([125I]BTX), [3H]pirenzepine ([3H]PRZ), and [3H]AFDX-384 ([3H]AFX) autoradiography. Unlike nicotine, cotinine failed to upregulate the expression of brain nicotinic receptors. Based on its relative safety in man, cotinine should prove useful in the treatment of diseases of impaired cognition and behavior without exhibiting the toxicity usually attributed to nicotine.