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The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of m-chlorophenylpiperazine.

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Abstract

m-Chlorophenylpiperazine (mCPP), a major metabolite of the atypical antidepressant trazadone, has been observed to produce marked physiological and behavioral effects in both humans and animals. These effects have been attributed to the interaction of mCPP with serotonergic receptors. The present study was designed to characterize those interactions of mCPP with central serotonergic receptors which mediate mCPP-induced stimulus control. A series of serotonergic antagonists (mesulergine, pizotyline, ketanserin, spiperone, risperidone, ritanserin, metergoline, pirenpirone, and LY53857) was tested for the ability to block the mCPP stimulus. The affinity of these antagonists for 5-HT2A and 5-HT2C receptors was then correlated with maximal percent inhibition of the mCPP stimulus. Kd at the 5-HT2C receptor was inversely proportional ($r = -0.75$, $P < 0.05$), and Kd at the 5-HT2A receptor directly proportional ($r = +0.67$, $P < 0.05$) to the maximal percent inhibition of the mCPP stimulus. The 5-HT2C selectivity ratio [Kd(5-HT2A)/Kd(5-HT2C)] of the antagonists was directly proportional ($r = +0.86$, $P < 0.01$) to maximal percent inhibition of the mCPP stimulus. A multiple regressions analysis indicated that 81% of the variance in the ability of a given antagonist to block the mCPP stimulus could be predicted on the basis of its affinity for 5-HT2A and 5-HT2C receptors. It is concluded that the stimulus effects of mCPP are mediated predominantly by a combination of agonist activity at 5-HT2C receptors and antagonist activity at 5-HT2A receptors.

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