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Ethanollike Properties of the Serotonergic Partial Agonist m-Chlorophenylpiperazine in Chronic Alcoholic Patients

To the Editor.—Alcoholic patients have lower levels of 5-hydroxyindoleacetic acid in cerebrospinal fluid[1]; decreased availability of the serotonin precursor, tryptophan[2]; and reduced serotonin concentrations in platelets.[3] These findings have led to the hypothesis that a dysregulation in serotonin metabolism may be involved in the pathogenesis of alcoholism. To further explore this hypothesis, we studied alcoholic patients who abstained from alcohol. Behavioral, physiological, and endocrine responses to the metabolite of trazodone hydrochloride, meta-chlorophenylpiperazine (m-CPP) hydrochloride, were used as indexes of serotonin receptor function in alcoholic patients.[4]

Twenty-one male patients who fulfilled *DSM-III-R* criteria for alcohol dependence and Research Diagnostic Criteria for alcoholism were selected for the study. They were in good physical health, euthymic, and abstinent from alcohol for at least 3 weeks when the study began. After written, informed consent was obtained, normal saline solution (the placebo) was administered intravenously. Thirty minutes later, m-CPP (0.08 mg/kg) was administered intravenously over 90 seconds. Objective behavioral ratings and self-ratings were obtained before and after infusion.

Eleven patients reported a "high" feeling comparable with the effect of alcohol after administration of m-CPP, but not after the administration of the placebo. The time course and magnitude of the effect varied among the subjects from a "buzz feeling" that lasted 10 minutes or less to a prolonged feeling of intoxication. Patient values using the National Institute of Mental Health's self-rating activation/euphoria subscale[4,5] showed significant increases following administration of m-CPP, but not following the administration of the placebo (change [mean ± SD] from the baseline value to the value 30 minutes after administration of the placebo: -1.55 ± 0.76; change from the value at the end of the placebo phase to the value 30 minutes after administration of m-CPP: 4.17 ± 1.84, $F[1,20] = 7.03$, by repeated-measures analysis of variance; $P < .02$). In addition, seven patients reported that m-CPP elicited an urge ("craving") to drink alcohol, while the placebo did not.

To our knowledge, this is the first report examining serotonergic responsivity to m-CPP in patients who abstained from alcohol. An m-CPP–induced "high" and craving to drink alcohol reported by a substantial number of alcoholic patients in our study add to evidence suggesting that serotonin is involved in the pathogenesis of at least certain types of alcoholism. This finding is also consistent with a recent drug discrimination study in rodents, which showed that the drug cue produced by trifluoromethylphenylpiperazine (a serotonin receptor agonist similar to m-CPP) generalized to that produced by ethanol.[6] If our results are substantiated, they will provide an additional rationale for using selective serotonin reuptake blockers, such as fluoxetine, in attempts to decrease the urge to drink in alcoholics.[7]

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