Behavioral and Neuroendocrine Responses to *m*-Chlorophenylpiperazine in Subtypes of Alcoholics and in Healthy Comparison Subjects

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Objective: *The purpose of this study was to explore central serotonergic functions in subgroups of alcoholics and in healthy comparison subjects.* *Method:* *The mixed serotonin (5-HT) agonist/antagonist* m-*chlorophenylpiperazine (m-CPP) was administered to male alcoholic patients who were classified according to the criteria of von Knorring et al. as type I alcoholics (late onset) (N=16) or type II alcoholics (early onset with antisocial traits) (N=24) and to 22 healthy comparison subjects. Psychological, physiological, and neuroendocrine measures were obtained before and after the m-CPP infusion.* *Results:* *m-CPP elicited subtype-related differential effects among the alcoholics; the type I alcoholics reported more anger and anxiety, and the type II alcoholics reported increased euphoria and a greater likelihood of drinking. The healthy comparison subjects exhibited a greater increase in plasma ACTH response to the m-CPP infusion than the alcoholics regardless of subtype.* *Conclusions:* *Differences in certain 5-HT receptor functions may explain some of the clinical characteristics that differentiate the type II and type I subgroups of alcoholic patients. Furthermore, alcoholics may have reduced sensitivity of 5-HT_{2C} receptors in comparison with healthy subjects.*

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Recently, we administered the serotonin (5-HT) uptake inhibitor clomipramine to a group of abstinent alcoholics and healthy volunteers. We found no significant differences in either behavioral or neuroendocrine responses between the groups (1). This lack of differences caused us to question whether alterations in 5-HT function previously thought to occur in alcoholism (2–7) might involve only certain types of 5-HT receptors or only subgroups of alcoholics. To elucidate these issues, we used the criteria of von Knorring et al. (8) to categorize alcoholics into type I and type II subgroups and studied the behavioral and neuroendocrine responses following the administration of the mixed 5-HT agonist/antagonist *m*-chlorophenylpiperazine (m-CPP) to a group of recently abstinent alcoholics and healthy comparison subjects.

The rationale for subtyping alcoholics is supported by a growing literature suggesting that alcoholism is a heterogeneous disorder. Bohman, Cloninger, and colleagues (9–11) studied patterns of alcohol abuse in Swedish subjects adopted away from their biological parents at an early age and used the terms "type I" and "type II" to describe two relatively homogeneous subgroups of alcoholics. Subsequent studies by von Knorring et al. (8), also conducted in Sweden, established operational clinical criteria to allow the subgrouping of alcoholics into mutually exclusive categories. According to these criteria, type II alcoholics have the onset of heavy drinking before the age of 25 and/or their first treatment before 30 years of age, as well as at least two social complications due to excessive consumption of alcohol. Subjects not meeting the type II criteria are considered to be type I.

Cloninger (12) also described personality traits characteristic of subgroups of alcoholics. He concluded that alcoholics exhibit a continuum of personality traits: type I alcoholics have passive-dependent, anxious traits, whereas type II alcoholics are more likely to exhibit antisocial traits coupled with impulsive and alcohol-seeking behaviors. Cloninger postulated that low harm avoidance, a personality characteristic of type II alcoholics, was associated with reduced central serotonergic function. This postulate is consistent with the findings of Ballenger et al. (2), who investigated a group of abstinent, young male alcoholics and found that they had a low concentration of 5-hydroxyindoleacetic acid (5-

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HIAA), the major metabolite of 5-HT, in their cerebrospinal fluid.

Our interest in m-CPP as a pharmacological probe to study 5-HT function was based, in part, on animal studies. In a drug discrimination paradigm, trifluoromethylphenylpiperazine (TFMPP), a close structural analogue of m-CPP, was perceived as alcohol by 70% of rats trained to discriminate ethanol from the vehicle (13). The discriminative cue was blocked when the rats were pretreated with parachlorophenylalanine, a 5-HT synthesis inhibitor (14). In addition, m-CPP has been extensively used to study 5-HT receptor sensitivity in both healthy comparison subjects and patients with a variety of psychiatric disorders, including obsessive-compulsive and panic disorders, depression, and schizophrenia (15, 16).

In the present parallel group study, we examined selected behavioral, neuroendocrine, and physiological responses after the sequential administration of intravenous placebo followed by m-CPP in alcoholics who had been abstinent and under close supervision on a locked research ward for at least 3 weeks and in healthy comparison subjects. The alcoholics were classified into types I and II according to the criteria of von Knorring et al. (8). We hypothesized that if type II alcoholics had reduced presynaptic central 5-HT function, they would exhibit an exaggerated neuroendocrine response to m-CPP, as do animals with presynaptic serotonergic lesions (17). In addition, we hypothesized that the 5-HT effects of m-CPP would result in differential behavioral effects, with type I alcoholics becoming more anxious and type II alcoholics exhibiting either alcohol-seeking behavior or euphoria. This postulate was based on the observation that m-CPP has frequently enhanced the expression of preexisting symptoms or traits in patients with panic or obsessive-compulsive disorders, schizophrenia, and migraine headaches (15, 16).

METHOD

Alcohol-dependent patients were admitted to the National Institute on Alcohol Abuse and Alcoholism research ward at the National Institutes of Health (NIH) Clinical Center. Both the alcoholic patients and the healthy comparison subjects underwent a clinical interview with a psychiatrist (D.T.G.) and a complete physical examination, including radiological and laboratory assessments, to make sure that they were in good physical health. Patients with elevated levels of liver enzymes or other chemical abnormalities were excluded from participation in the study. The Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (18) and the Michigan Alcoholism Screening Test (MAST) (19) were administered to all of the patients. Only patients meeting the Research Diagnostic Criteria (20) for alcoholism and the DSM-III-R criteria for alcohol dependence were included in the study. Potential subjects with a history of any intravenous drug use or current or recent drug abuse, seizures, major head trauma (defined as a period of unconsciousness exceeding 1 hour), panic disorder, obsessive-compulsive disorder, manic-depressive illness, or schizophrenia were excluded from participation. All patients were free of medications, illicit drugs (ascertained through negative urine drug screens), and alcohol (ascertained through daily supervision and random breath alcohol measurements) for a minimum of 3 weeks before the study. While hospitalized, all patients attended daily Alcoholics Anonymous meetings and were involved in group, family, and recreational therapies as well as educational seminars on alcoholism.

Using the criteria set forth by von Knorring et al. (8), we divided the alcoholic patients into type I (N=16) and type II (N=24) subgroups on the basis of information obtained from the SADS-L and the MAST. Patients in whom the onset of heavy drinking occurred before the age of 25, and/or whose first treatment for alcoholism occurred before age 30, and who had at least two social complications associated with alcohol abuse (e.g., violence or domestic problems while intoxicated, absence from work, or legal difficulties) were classified as type II. Patients not meeting the type II criteria were classified as type I. Classification according to type was done by a research social worker (D.W.) who was blind to the results of the m-CPP challenge. Psychiatrists in attendance during the m-CPP infusion were blind to the subgrouping of the alcoholics.

The healthy comparison subjects (N=22) were free of any axis I or II psychiatric diagnoses, were taking no medications, had been alcohol free for at least 1 week before the study, and had no first-degree relatives with alcohol abuse or dependence.

Written informed consent was obtained from all subjects before participation in the study.

Procedure

To reduce confounding effects of diet on serotonin metabolism, all participants received a low-monoamine diet for a minimum of 3 days before the study. Then, after overnight bed rest and fasting, the subjects had intravenous cannulas placed in both arms. One was used for blood sampling and the other for m-CPP administration; both were kept open with a slow intravenous infusion of normal saline. Following a stabilization period of at least 1 hour, baseline behavioral ratings, oral temperature, blood pressure, heart rate (measured by an automated Dinamapp recorder), and blood for neuroendocrine measures were obtained. Subjects were told that they would receive either drug or placebo followed by the other agent. They were instructed to inform the attending physician and nurse about any changes in how they felt during the administration of the agents.

Twenty milliliters of normal saline were infused intravenously over 90 seconds, followed 30 minutes later by m-CPP (0.08 mg/kg) diluted in 20 ml of physiological saline infused over 90 seconds. (m-CPP was obtained from Aldrich Pharmaceutical Co., Milwaukee.) The identity and purity of the m-CPP were verified by the NIH Pharmaceutical Development Services with the use of high-performance liquid chromatography. The dosage of 0.08 mg/kg of m-CPP was chosen to maximize the hormonal response and to avoid panic attacks, which had been previously reported to occur when 0.1 mg/kg of m-CPP was infused intravenously over 20 minutes in normal subjects (21). The rate of infusion was the same as in previous studies with intravenous m-CPP (22). The intravenous route of administration was chosen to avoid interindividual differences in absorption that follow oral administration. Blood pressure, heart rate, and ACTH concentrations were measured at baseline, 30 minutes after the first (saline) injection, and 10, 20, 30, 40, 50, 60, 90, and 120 minutes after the m-CPP infusion. m-CPP concentrations were quantified at 1-minute intervals after m-CPP infusion for 5 minutes and then at the above-mentioned times, according to the method of Murphy et al. (22). Blood samples were immediately placed on ice and then centrifuged within 3 hours of collection; plasma was separated and stored at –70 °C. Concentrations of ACTH were determined by Hazleton Laboratories in Vienna, Va., with the use of radioimmunoassay techniques.

The Hamilton Depression Rating Scale (23) and the trait portion of the Spielberger State-Trait Anxiety Inventory (24) were administered before the start of the study. Behavioral ratings were obtained at baseline, 30 minutes after the first injection, and 30, 60, 90, and 120 minutes after the m-CPP infusion. Subjects were instructed to complete ratings of the magnitude of the drug effect since the last rating. Ratings included 1) a modified version of the National Institute of Mental Health self-rating scale assessing changes in mood (22) (scored 0–6); 2) an observer-rated global scale assessing sadness, anxiety, euphoria, arousal, irritability, and functional impairments; 3) the state portion of the Spielberger State-Trait Anxiety Inventory (24); and 4) a self-rating scale (scored 0–6) assessing the patient's response during the infusion to the following questions: How much did you crave a drink? How drunk or intoxicated did you feel? How likely would you have been to take a drink of alcohol?

TABLE 1. Characteristics of Alcoholics Grouped According to Subtypes

Variable	Type I Alcoholics (N=16) Mean	Type I Alcoholics (N=16) SD	Type II Alcoholics (N=24) Mean	Type II Alcoholics (N=24) SD	Analysis t (df=38)	Analysis p
Current age (years)	45.1	7.1	35.9	9.7	3.2	<0.01
Michigan Alcoholism Screening Test score	32.4	7.6	40.8	6.4	–3.8	<0.001
Age at onset of heavy drinking (years)	33.2	10.2	21.2	6.8	4.5	<0.001
Quantity of alcohol consumed (grams per occasion in last 6 months)	177.4	132.7	257.4	88.2	–2.3	<0.03
Frequency of drinking (days in last 6 months)	106.3	54.0	131.5	55.0	–1.4	0.16
Years of excessive alcohol consumption	9.9	5.9	17.2	9.0	–2.9	<0.01
Days since last drink	36.9	11.8	38.3	22.0	–0.2	0.83

We used a single-blind design for the administration of m-CPP. This decision was based on our interest in comparing m-CPP-induced differences between groups and our previous results with another serotonergic challenge study (1) that used clomipramine, which revealed no behavioral or biochemical effects following placebo in similarly defined groups of alcoholics and healthy comparison subjects. The fact that the subjects were blind to the drug condition, that the raters were blind to the alcoholics' subgrouping, and that there were no statistically significant effects resulting from the placebo infusion make it unlikely that the study design biased the results.

Data Analysis

Because of the large number of tests performed, a significance level of $p<0.01$ was chosen, except for the three a priori hypotheses, for which $p<0.05$ was used. Placebo effects were examined for all variables with the use of a two-way repeated measures design with one group factor and one time factor. The time factor consisted of two points 30 minutes apart. Effects of m-CPP were examined for all variables by means of a two-way repeated measures design with one group factor, one time factor, and one covariate consisting of the baseline value measured immediately before the m-CPP infusion. Greenhouse-Geisser corrections for significance levels were used where appropriate. All of the analyses in this study were performed with the BMDP software (25).

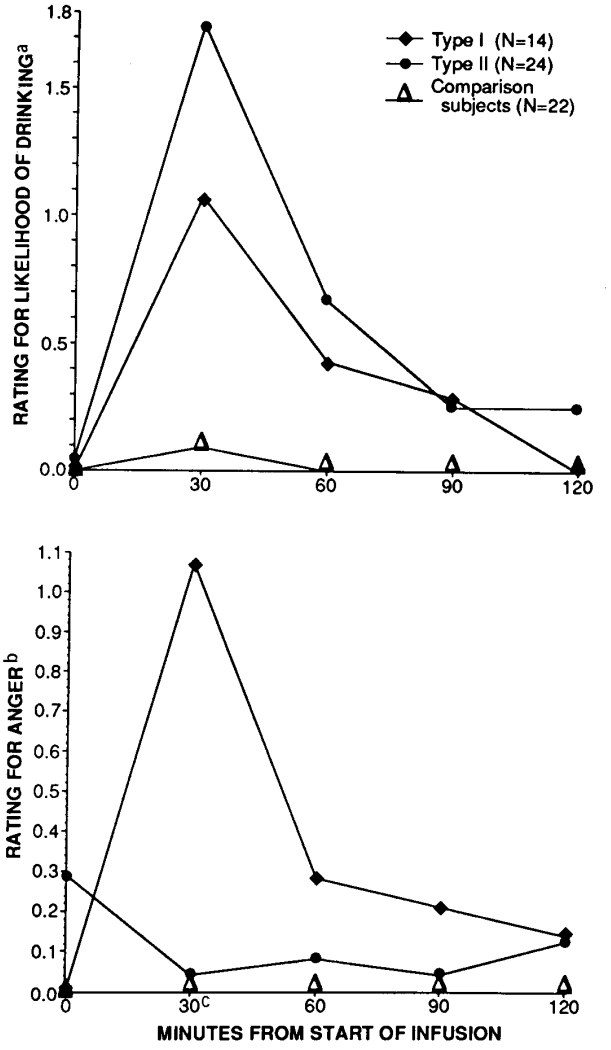
RESULTS

The type I alcoholics were older, had lower MAST scores, started to consume excessive amounts of alcohol later in life, consumed less alcohol per drinking occasion, and had fewer years of excessive alcohol consumption than the type II alcoholics (table 1). Only one type I and two type II alcoholics met the Research Diagnostic Criteria for a drug use disorder during their lifetime.

Hamilton depression scale ratings revealed that the groups were essentially depression free, with mean scores of 1.3 (SD=0.4) for the healthy comparison subjects, 2.6 (SD=0.6) for the type I alcoholics, and 3.7 (SD=0.7) for the type II alcoholics. The anxiety measure showed a group difference ($F=7.3$, $df=2, 59$, $p<0.001$), with both type I and type II alcoholics having higher trait anxiety ratings (mean=35.0, SD=1.7, and mean=36.9, SD=1.9, respectively) than the comparison subjects (mean=28.4, SD=1.4).

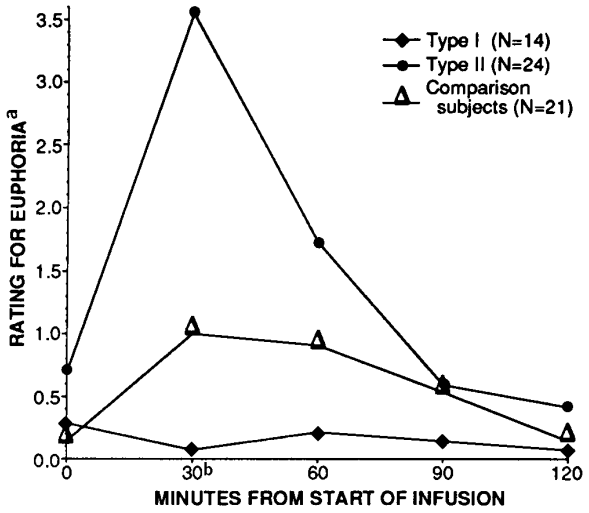
There were no significant differences among the groups in any of the neuroendocrine, physiological, or behavioral variables either at baseline or after placebo infusion (data not shown). Similarly, there were no significant correlations between any placebo effect and the

FIGURE 1. Effects of m-CPP on the Likelihood of Drinking and on Anger in Type I and Type II Alcoholics and Healthy Comparison Subjects



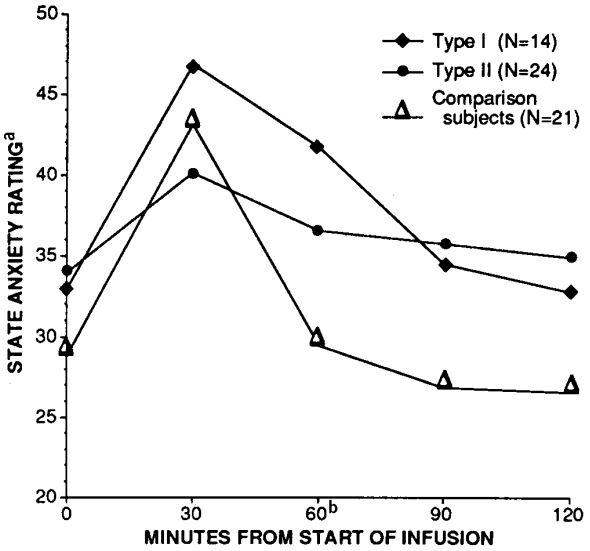
[a]Significant group differences ($F=6.2$, $df=2, 57$, $p=0.004$); effect for type II alcoholics significantly greater than that for comparison subjects ($t=3.5$, $df=57$, $p<0.001$).
[b]Significant time-by-group interaction ($F=6.3$, $df=6, 171$, $p<0.001$).
[c]Significant group differences ($F=8.1$, $df=2, 58$, $p<0.001$); effect for type I alcoholics significantly greater than that for type II alcoholics ($t=3.6$, $df=58$, $p<0.001$) and for comparison subjects ($t=3.7$, $df=58$, $p<0.001$).

FIGURE 2. Effects of m-CPP on Ratings of Euphoria in Type I and Type II Alcoholics and Healthy Comparison Subjects



[a]Significant time-by-group interaction (F=4.7, df=6, 162, p=0.003).
[b]Significant group differences (F=8.0, df=2, 58, p<0.001); effect for type II alcoholics significantly greater than that for type I alcoholics (t=–3.7, df=58, p<0.001) and for comparison subjects (t=3.0, df=58, p<0.01).

FIGURE 3. Effects of m-CPP on State Anxiety Ratings in Type I and Type II Alcoholics and Healthy Comparison Subjects



[a]Significant time-by-group interaction (F=3.9, df=6, 168, p=0.01).
[b]Significant group differences (F=5.6, df=2, 56, p<0.01); effect for type I alcoholics greater than that for type II alcoholics (t=2.1, df=56, p<0.05) and for comparison subjects (t=4.9, df=56, p<0.001), and effect for type II alcoholics greater than that for comparison subjects (t=3.2, df=56, p<0.01).

corresponding variables measured 30 minutes after the m-CPP infusion.

Samples obtained after m-CPP infusion from a randomly selected group of 41 subjects, representative of all the groups, demonstrated measurable plasma concentrations of m-CPP. Body temperature, a physiological response to m-CPP administration, showed a uniform 0.2 °C rise from baseline for all groups after m-CPP infusion, with a significant time effect (F=5.45, df=7, 336, p=0.001).

The m-CPP infusions produced significant group differences on three behavioral measures. The top part of figure 1 shows a significant group difference in the likelihood of drinking, with the type II alcoholics showing a significantly greater likelihood than the healthy comparison subjects. The bottom part of figure 1 shows significant group differences in anger 30 minutes after m-CPP, with the type I alcoholics reporting significantly more anger than the type II alcoholics and the comparison subjects.

Figure 2 shows significant group differences in euphoria 30 minutes after m-CPP, with the type II alcoholics reporting significantly more euphoria than the type I alcoholics and the healthy comparison subjects.

Figure 3 shows that there were significant group differences in anxiety 60 minutes after m-CPP, with the type I alcoholics having significantly higher anxiety ratings than both the type II alcoholics and the healthy comparison subjects. At 60 minutes the type II alcoholics' ratings were also significantly higher than those of the comparison subjects.

In an attempt to understand how the onset of a mood change brought about by m-CPP might relate to each patient's desire to drink alcohol, we examined the co-occurrence of likelihood of drinking alcohol with m-CPP-induced anger, euphoria, and anxiety. Among the 15 type II alcoholics who reported an increased likelihood of drinking, 11 reported euphoria, eight anxiety, and three anger. There was a positive correlation between euphoria and the likelihood of drinking (r=0.52, N=24, p<0.05). Among the six type I alcoholics who reported an increased likelihood of drinking, two reported euphoria, five anxiety, and four anger. Correlations between anger and anxiety (r=0.80, N=16, p<0.01), anger and the likelihood of drinking (r=0.73, N=16, p<0.01), and anxiety and the likelihood of drinking (r=0.67, N=16, p<0.01) were also significant. There were no significant correlations between behavioral measures (e.g., euphoria, anger, state anxiety, likelihood of drinking) and duration of heavy drinking. The one healthy comparison subject who reported an increased likelihood of drinking did not report an increase in any other behavioral measure. The healthy comparison subjects showed no significant correlations between affective responses and the likelihood of drinking. There was no significant m-CPP effect on the item reflecting how drunk or intoxicated the subjects felt.

Figure 4 shows a significant group difference in plasma ACTH 10 minutes after the m-CPP infusion, with the healthy comparison subjects having a significantly greater increase in ACTH than the alcoholics. There was no significant correlation between ACTH response and duration of heavy drinking.

There was a significant group-by-time interaction for heart rate (F=2.5, df=14, 308, p=0.007), with the healthy

comparison subjects showing a 3-bpm increase within 10 minutes after the m-CPP infusion and the type I alcoholics showing a 3-bpm increase 40 minutes after the infusion. The type II alcoholics did not show any changes in heart rate in response to the infusion. There were no group differences in either systolic or diastolic blood pressure in response to the infusion.

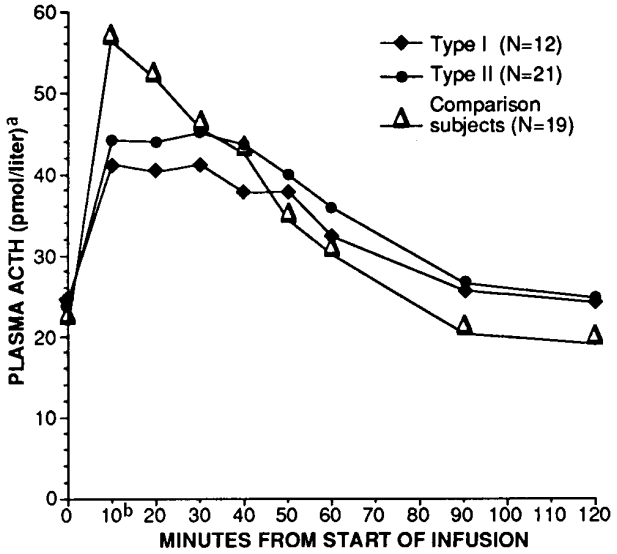
DISCUSSION

The administration of m-CPP resulted in a significant drug effect with measurable increases in temperature, heart rate, and plasma concentrations of m-CPP and ACTH. The m-CPP-induced significant increase in the likelihood of drinking reported by the type II alcoholics corroborates the results of our preliminary report (26), corroborates the findings of a recent study by Krystal et al. (27) showing that the administration of m-CPP to a group of alcoholics resulted in a significant increase in "craving" for alcohol, and is consistent with an animal drug-discrimination study (13) showing that TFMPP, a close structural analogue of m-CPP, resulted in alcohol-like effects. By categorizing the alcoholics into subtypes, we were able to extend these earlier findings and show a differential effect of m-CPP in the alcoholic subgroups, with the type II alcoholics reporting both a greater likelihood of drinking and more euphoria and the type I alcoholics reporting more anger and anxiety. These differences between subgroups of alcoholics give further support to the concept that alcoholism is a heterogeneous disorder.

The behavioral differences between the alcoholic subgroups appeared to arise from an interaction between the criteria used to subgroup the alcoholics and the effects of the m-CPP challenge. The criteria of von Knorring and co-workers for subgrouping alcoholics (8) rely primarily on the age at onset of subjective alcohol-related problems and secondarily on social complications resulting from the abuse of alcohol. The emphasis on the age at onset of problem drinking is consistent with other studies showing that this clinical variable is an important discriminating factor in the subtyping of alcoholics (28–30). Although the biological concomitants associated with age at onset, as well as social complications of alcoholism, remain uncertain, it appears, on the basis of the findings in this study, that they may involve 5-HT.

Previously (1), we administered clomipramine, a relatively selective 5-HT uptake inhibitor, as a single, low-dose, intravenous infusion to subgroups of alcoholics defined according to the criteria of von Knorring et al. It produced no differences in behavioral or endocrine responses between healthy comparison subjects and alcoholics. This suggests that the behavioral changes observed in the present study are unlikely to have been the result of a global perturbation of central 5-HT but, rather, arose secondary to the effects of m-CPP. The mechanism whereby m-CPP might induce these behavioral effects remains speculative, since m-CPP has high affinity for a number of 5-HT receptors: (in order of decreasing affinity) 5-HT_{2C} (formerly 5-HT_{1C}) (31), 5-HT_3, 5-HT_{2A}, 5-HT_{1A} (32–34), 5-HT_7, and 5-HT_6 (35, 36). At high concentrations it also binds to non-5-HT receptors and to the human 5-HT transporter (37). It is an agonist at 5-HT_{2C} sites but an antagonist at 5-HT_{2A} and 5-HT_3 sites (33, 34, 38, 39).

FIGURE 4. Effects of m-CPP on Plasma ACTH Concentrations in Type I and Type II Alcoholics and Healthy Comparison Subjects



[a]Significant time-by-group interaction (F=3.2, df=14, 343, p=0.01).
[b]Significant group differences (F=4.5, df=2, 54, p=0.02); effect for comparison subjects significantly greater than that for the combined alcoholic groups (t=–2.1, df=54, p<0.05).

Consistent with the postulates of Cloninger (12) and our hypothesis, the type II alcoholics reported a greater feeling of euphoria in comparison with both the type I alcoholics and the healthy subjects. This difference did not appear to result from differences in alcohol consumption between the groups, since there were no significant correlations between the level or duration of excessive consumption and any of the significant behavioral effects. The association of the likelihood of drinking with euphoria among the type II alcoholics and with anger and anxiety among the type I alcoholics raises the possibility that these affective responses might serve as a priming cue to trigger the desire to drink. The possibility that the stress of having an intravenous infusion or external stimuli in the testing room might have triggered an increased likelihood of drinking is unlikely, since there were no significant effects secondary to the placebo infusion, and all subjects underwent the study in similar hospital rooms devoid of any obvious cues associated with the consumption of alcohol.

The type I alcoholics, when challenged with m-CPP, showed more anxiety and anger than the type II alcoholics. This is again consistent with our hypothesis that type I alcoholics would demonstrate more m-CPP-induced anxiety. The mechanism of action by which m-CPP induces anxiety remains unclear. On the basis of

data from social interaction studies in animals, it may involve the 5-HT_{2C} receptor (40, 41). This conclusion is also supported by limited data from the use of nonspecific 5-HT_1 and HT_2 antagonists (metergoline and ritanserin) in combination with m-CPP in humans (42–44). The association between anger, anxiety, and the desire to drink demonstrated by the type I alcoholics again raises the possibility that mood changes might have triggered the desire to drink.

Previous studies have reported that the 5-HT_2/5-HT_{2C} receptor agonist MK-212 (45) as well as m-CPP can give rise to an ethanol-like subjective feeling state. On the basis of the findings of Krystal et al. (27), the ethanol-like effect does not appear to be specific for ethanol only but may also be similar to cues produced by marijuana or cocaine. In the present study we did not address the issue of whether m-CPP mimics other drugs of abuse (e.g., marijuana, cocaine), since patients currently or recently abusing these drugs were excluded from the study. We did, however, ask the subjects how drunk or intoxicated they felt after the m-CPP infusion. This question was intended to ascertain whether m-CPP had any intoxicating ethanol-like effects, and it is interesting that there was no significant drug effect on feeling drunk or intoxicated. Thus, the m-CPP cue mimics only certain effects of ethanol, such as euphoria.

The m-CPP infusion resulted in a significant rise in plasma ACTH. This finding is consistent with previous studies (22, 46) that have reported similar hormonal changes following 5-HT agonist challenges. The lack of a difference in ACTH response between the subgroups of alcoholics does not support our original hypothesis. Furthermore, it suggests that the receptors controlling ACTH release after a low-dose m-CPP infusion may be different from those which are involved in controlling the behavioral responses to m-CPP. The blunted ACTH response in alcoholics is consistent with previous studies which showed that alcoholics have an attenuated ACTH response to both corticotropin-releasing hormone (47) and insulin (48) challenges. It is unlikely, however, that the decreased ACTH response represents hypothalamic or pituitary damage due to alcohol, since we found in a previous study (49) that the metabolic stressor 2-deoxy-D-glucose gave rise to an exaggerated ACTH response in a similar group of alcoholics compared with healthy subjects. The lack of a relationship between ACTH response and euphoria after the m-CPP infusion is seemingly at variance with the findings of Lukas and Mendelson (50), who reported that the rise in ACTH induced by alcohol was correlated with euphoria.

In interpreting these results, it should be noted that the study was conducted without a separate placebo day, that some of the alcohol-related outcome measures have not been validated, and that the m-CPP effects on anger and the likelihood of drinking were relatively small. As we stated in the Method section, we do not feel that the study design substantially biased the results. We acknowledge that the current methods of measuring changes in affective and motivational states are imprecise and should be the focus of future research.

The clinical criteria used in this study to classify alcoholics into subgroups represent only one of many possible approaches (28–30, 51). While the criteria of von Knorring et al. (8) use well-defined clinical information to subgroup alcoholics, it is noted that these criteria (e.g., age at onset of alcoholism and social complications) remain somewhat imprecise and are subject to biases in recall. In contrast, the typology proposed by Babor et al. (29) is more comprehensive (e.g., type A alcoholics have later onset, fewer childhood risk factors, less severe dependence, and fewer alcohol-related problems, whereas type B alcoholics have more childhood risk factors, more familial alcoholism, an early onset of alcohol-related problems, a greater severity of dependence, polydrug use, and more psychopathology) and, if operationalized for clinical research, may lead to more accurate subtyping of alcoholics.

In conclusion, the administration of an m-CPP infusion resulted in differential behavioral effects in subgroups of alcoholics, with type I alcoholics reporting more anger and anxiety and type II alcoholics reporting increased euphoria and a greater likelihood of drinking. These findings, together with those of our recent study (52) showing that early-onset alcoholics have lower CSF concentrations of the main 5-HT metabolite 5-HIAA than late-onset alcoholics, support the concept that differences in central serotonergic functions may be important concomitants of age at onset and impulsive antisocial traits in alcoholics. These serotonergic differences may provide a rationale for developing pharmacological and psychotherapeutic interventions that are specific for subtypes of alcoholics.

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