Alcohol Abolishes the Hypotensive Effect of Clonidine in Spontaneously Hypertensive Rats

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Abstract This study tested the hypothesis that concurrent ethanol administration attenuates the hypotensive effect of clonidine. Four groups of spontaneously hypertensive rats matched for baseline systolic blood pressure and body weight were randomly assigned the following treatments: (1) water (control), (2) ethanol, (3) clonidine, and (4) ethanol plus clonidine for 13 weeks. Ethanol was provided in the drinking water as 5% for 1 week, 10% for the next 2 weeks, and 20% from week 4 to 13. Starting from similar baseline systolic blood pressures, the blood pressure of the control group increased 10 to 15 mm Hg over the 13-week treatment period. A similar rise in systolic blood pressure occurred in ethanol-treated rats despite a dramatic (40% to 50%, P<.05) reduction in fluid intake. Clonidine (300 μg/kg per day) caused a smaller and shorter reduction in fluid intake. The fluid intake of the combined treatment group was similar to that of the ethanol group. Either treatment caused a significant and additive reduction in body weight gain. Treatment-related mortality (20%) occurred only in the combined treatment group by the 12th week. Clonidine elicited a slowly developing hypotensive response (P<.05) that started 2 to 3 weeks after treatment was initiated and lasted throughout the treatment period. Ethanol abolished the hypotensive effect of clonidine and resulted in blood pressure values that were not significantly different from those of the control or the ethanol groups. Blood ethanol concentration was similar in the presence or absence of clonidine (5.5±1.9 versus 6.5±3 mmol/L). We investigated whether long-term ethanol administration attenuates the hypotensive response elicited by centrally administered clonidine. The dose-response curve depicting the hypotensive responses to intracisternal clonidine in the ethanol-treated group was significantly shifted upward compared with that of the control group. We conclude the following: (1) ethanol coadministration abolishes the hypotensive effect of clonidine in conscious SHR; (2) ethanol-induced reduction in fluid intake whether given alone or in combination with clonidine may have masked its pressor effect; (3) ethanol and clonidine exert an additive inhibitory effect on body weight gain; and (4) ethanol adversely influences the activity of the central pathways involved in the hypotensive response to clonidine. (Hypertension. 1994;24:802-807.)

Key Words • alcohol • clonidine • antihypertensive therapy • rats, inbred SHR

In a previous study we showed that short-term ethanol administration elicited an immediate reversal of the hypotensive response to clonidine in conscious, unrestrained spontaneously hypertensive rats (SHR).1 This adverse effect of ethanol seems to be targeted against centrally acting hypotensive drugs. In support of this view is the finding that a similar hemodynamic interaction occurs between ethanol and another centrally acting drug, guanabenz.2 The hemodynamic interaction is dose related2 and involves ethanol doses that are likely to be consumed clinically and lead to blood ethanol concentrations compatible with low to moderate intoxication. Interestingly, in the dose range used in these studies,1,2 ethanol elicited little or no change in the baseline arterial pressure of rats1,3,4 and humans.5,6 Furthermore, pharmacological and biochemical evidence suggests that the interaction involves a centrally mediated sympathoexcitatory action of ethanol.2 This latter effect may explain the immediate reversal by ethanol of the hypotensive response of centrally acting drugs that is the consequence of an inhibition of central sympathetic tone.7

Regular alcohol use, which has been reported in a substantial proportion of treated hypertensive individu-
In the present study, we investigated the possibility that concurrent long-term alcohol intake may attenuate the hypotensive response elicited by clonidine. To achieve this goal, we gave different groups of SHR clonidine, ethanol, or clonidine plus ethanol in drinking water and compared the responses with those of a control (water) group for 13 weeks. We compared changes in fluid intake and body weight along with tail blood pressure over the 13-week treatment period. We also tested the hypothesis that long-term ethanol administration adversely influences the function of the central structures implicated in the hypertensive effect of clonidine. To investigate this possibility, we evaluated the hypotensive and bradycardic responses elicited by centrally (intracisternally) administered cumulative doses of clonidine in conscious, unrestrained, ethanol-treated SHR and compared them with control responses. In the latter study, we used clonidine doses that had no effect when administered systemically but lowered blood pressure when administered intracisternally.

**Methods**

Male SHR (Charles River Breeding Laboratories, Raleigh, NC) weighing approximately 300 g were used in this study. The animals were acclimated to the facility and to tail-cuff blood pressure measurements for at least 1 week before the study. Baseline systolic blood pressures and body weights were matched for when the rats were divided into four groups of 10 rats each. The rats of each group were randomly assigned one of the following treatments in their drinking water and had constant access to Purina Lab Chow: (1) no treatment (control), (2) clonidine, (3) ethanol, or (4) clonidine plus ethanol. The method of ethanol feeding was that of Chan and Sutter, who 21 added to the drinking water as 5% (vol/vol) for the first week, 10% for the next 2 weeks, and 20% from weeks 4 to 13. During this regimen, average daily ethanol consumption was 8 to 10 g/kg. Clonidine was provided alone or in combination with ethanol in the amount of 300 µg/kg per day as described elsewhere. 24 The clonidine concentration was adjusted in relation to fluid intake so that the average daily dose was similar in the clonidine and clonidine plus ethanol groups. Blood pressure was measured weekly by the tail-cuff method as in our previous studies 22 23 using a pneumatic tail-cuff apparatus (ITTC Laboratories) through week 12 and by direct method at week 13. Fluid intake was measured daily, and body weights were recorded every week. All surgical procedures were approved by the institutional Animal Care and Use Committee and were conducted in accordance with institutional and National Institutes of Health guidelines.

**Surgical Procedure**

At the end of the 13-week treatment period, rats were chronically instrumented for direct measurements of blood pressure and heart rate, which were performed in conscious, unrestrained rats as in our previous studies. 24 25 Briefly, rats were instrumented with chronic indwelling catheters for blood pressure recording and intravenous drug administration 2 to 3 days before the experiment. With rats under methohexitol (Brevil, Eli Lilly; 50 mg/kg IP) anesthesia, arterial and venous catheters (PE-50) were advanced to the abdominal aorta and vena cava, respectively, from the femoral vessels. The distal ends of these catheters were plugged with stainless steel pins and guided subcutaneously to the back of the neck and exteriorized. The incision was closed, 60 000 U IM of penicillin G benzathine and penicillin G procaine (Durapen; Vedco, Inc) was administered, and the rat was kept warm until recovery. Each rat was then housed in an individual cage. Two to 3 days were allowed for recovery from surgery and for acclimatization to the environment; studies were performed while rats rested unrestrained in their home cages.

**Blood Ethanol Concentration**

A volume of 0.1 mL of blood was drawn through the arterial catheter on the morning of the experiment. The ethanol content of the samples was measured by the enzymatic method described by Bernt and Guttmann 26 and used in our previous studies. 27

**Intracisternal Administration**

Three days before intravascular catheterization (ie, 5 to 6 days before the experiment), rats in the ethanol and water (control) groups were prepared for intracisternal drug administration as in our previous studies. 20 With rats under methohexitol anesthesia (50 mg/kg IP), a stainless steel guide cannula (23G, Small Parts) was passed between the occipital bone and cerebellum so that its tip protruded into the cisterna magna. The cannula was secured in place with small metal screws and dental acrylic cement (Durelon, Thompson Dental Supply) as described by others. 27 The guide cannula was considered patent when spontaneous outflow of cerebrospinal fluid was observed and by gross postmortem histological verification following injection of the same volume of fast green dye (EM Science). After intracisternal cannulation, rats received penicillin G benzathine and penicillin G procaine (60 000 U IM; Durapen; Vedco, Inc) and were housed individually.

**Blood Pressure and Heart Rate Recording**

On the day of the experiment, rats were allowed to acclimate to the experimental setting for at least 30 minutes. Phasic blood pressure was recorded by connecting the arterial catheter of the conscious rat to a Statham pressure transducer (P23 DC), and basal blood pressure was displayed on a polygraph (model 7D, Grass Instrument Co). Heart rate was computed from the blood pressure pulse by a Grass tachograph and was displayed simultaneously on another channel of the polygraph. Both blood pressure and heart rate were allowed to stabilize at basal levels for at least 30 minutes.

** Hemodynamic Responses Elicited by Intracisternal Clonidine in Conscious Rats**

This experiment investigated whether long-term (13-week) ethanol administration attenuates the centrally (intracisternal) mediated hypotensive and bradycardic responses elicited by acutely administered clonidine. Cumulative dose-response curves were constructed in the ethanol and control (water) groups as described in our previous study 27 and elsewhere. 28 Clonidine was injected intracisternally in a cumulative dose fashion (0.02, 0.1, 0.5, 2.5, and 12.5 µg) after stabilization of blood pressure and heart rate at baseline. The injections started with the smallest dose, and each subsequent dose was injected every 10 minutes intracisternally into conscious, unrestrained rats. The volume injected for any given dose did not exceed 5 µL and was delivered over 10 seconds. Injections of equal volumes of saline had no effect on blood pressure and heart rate. The intracisternal injections were made by inserting a 30-gauge stainless steel cannula (Small Parts) into the guide cannula with its tip protruding 0.5 to 1 mm below the tip of the guide cannula. The dose-related hypotensive and bradycardic responses elicited by intracisternal clonidine in the control and ethanol-fed rats were compared. The smaller dose (0.02 to 0.5 µg) of clonidine had no effect on blood pressure and heart rate when injected intravenously (data not shown).

**Statistical Analysis**

Values given are mean±SEM. Student's t test was used in the analysis of paired and unpaired means with the level of significance chosen at P<0.05. The time-course data were analyzed by repeated measures ANOVA followed by multiple comparison post hoc tests (Student-Newman-Keuls). These analyses were performed by INSTAT MAC INSTANT STATISTICS (GraphPad Software). Mean arterial pressure was calculated as...
Their combination on daily fluid intake in spontaneously hypertensive rats (n=10 in each group). Values are mean±SEM. Differences between treatment and control groups were assessed by repeated measures ANOVA. Statistically significant differences (P<.05) between different treatments are indicated by the letters a through d. a indicates P<.05 compared with control; b, P<.05, clonidine+ethanol vs clonidine; c, P<.05, clonidine+ethanol vs ethanol; and d, P<.05, clonidine vs ethanol. BL indicates baseline.

**Results**

The rats in the four groups exhibited similar baseline systolic blood pressure, body weight, and daily fluid intake (Figs 1 through 4). The addition of clonidine, ethanol, or their combination to the drinking water caused a significant reduction in fluid intake and body weight. However, clonidine-evoked reduction in fluid intake was significantly (P<.05) less than that evoked by ethanol and lasted only 5 weeks versus the duration of the study in the case of ethanol (Fig 1). The fluid intake of the group that received the drug combination was not significantly different from that of the ethanol group (Fig 1), indicating that the drastic reduction in fluid intake in both groups was the result of ethanol treatment. Whether ethanol and clonidine were given alone or in combination, the average daily intake of ethanol was 8 to 10 g/kg and that of clonidine was approximately 300 µg/kg. Blood ethanol concentrations on the morning of the experiment were similar in the two groups that received ethanol alone and ethanol plus clonidine (5.5±1.9 and 6.5±3 mmol/L, respectively). Ethanol was not detectable in the blood of the control and clonidine groups. Fig 2 shows the effects of the different treatments on body weight gain. Compared with the control group, clonidine, ethanol, or their combination suppressed body weight gain over the treatment period. The differences between the treatment groups and the control group reached statistical significance by the fifth week and continued throughout the treatment period (Fig 2). Unlike the case with fluid intake, clonidine elicited a greater suppression in body weight gain compared with ethanol, and the inhibitory effect of both agents was additive (Fig 2).

**Blood Pressure Responses**

There were no significant differences in baseline systolic blood pressures measured by the tail-cuff method of all rats at the beginning of the experiment (Fig 3). Although the rats were hypertensive at the beginning of the experiment, the systolic blood pressure of the control (water) group rose 15 to 20 mm Hg above the baseline during the course of the study (Fig 3). Compared with the control group, the clonidine group exhibited significantly (P<.05) lower blood pressure starting from the third week of treatment (a difference of 22 mm Hg) (Fig 3). The hypotensive response elicited by clonidine was time dependent, and by week 13 the blood pressure of the clonidine group was 43 mm Hg lower (P<.05) than that of the control group. The clonidine dose (300 µg/kg per day) administered alone or in combination with ethanol throughout the study was the same. This was achieved by adjusting the clonidine concentration in relation to daily fluid intake. Similarly, the amount of
ethanol (8 to 10 g/kg per day) consumed alone or in combination with clonidine was similar. Over the 13-week experimental period, systolic blood pressure of the ethanol-fed SHR behaved in a manner similar to that of the control group, except for weeks 12 and 13, during which there was a tendency for the blood pressure of the ethanol group to be lower than that of the control group; however, the difference was not significant (Fig 3). Fig 3 also shows the influence of the concurrent administration of ethanol and clonidine on the blood pressure of SHR. Ethanol coadministration abolished the hypotensive effect of clonidine (Fig 3). The blood pressure of the combined treatment group was not significantly different from that of the control or ethanol group throughout the 13-week treatment period (Fig 3). The blood pressure of the combined treatment group was always higher than that of the clonidine group, and the difference reached statistical significance ($P<.05$) starting at week 5 through the remainder of the study except for week 7 (Fig 3). Only the combined treatment group lost rats, with two rats from this group dying by the end of week 13. Both rats exhibited an appreciable loss in body weight (50 g each within a week) and had sores on their feet. Because both rats were so weak, systolic blood pressure could not be measured in them at week 13.

**Effect of Ethanol on Centrally Mediated Hypotensive Responses**

This experiment investigated the influence of long-term (13-week) ethanol consumption on the hypotensive and bradycardic responses elicited by intracisternally administered clonidine in conscious unrestrained SHR. Cumulative administration of clonidine (0.02 to 12.5 μg IC) elicited dose-related hypotensive and bradycardic responses in the control (water) and ethanol-fed rats (Fig 4). However, the hypotensive response elicited by intracisternal clonidine in the ethanol-fed rats was significantly attenuated compared with the responses of the control rats with the doses of 0.5, 2.5, and 12.5 μg (Fig 4). Similarly, the bradycardic responses were attenuated in the ethanol-fed SHR at the two higher doses (Fig 4).

The dose of 0.5 μg clonidine, which elicited a significant reduction in blood pressure in the control rats but not in the ethanol-fed rats ($-22±2.9$ versus $-6±7.9$ mm Hg, $P<.05$), had no significant effect on blood pressure when administered intravenously (data not shown). These findings demonstrate the ability of chronically administered ethanol to interfere with the central structures that mediate the hypotensive effect of clonidine.

**Discussion**

The present study tested the hypothesis that concurrently administered alcohol attenuates the hypotensive effect of clonidine. Furthermore, the possibility was investigated that this adverse hemodynamic interaction is a consequence of ethanol-evoked changes in the function of the central nervous system pathways that mediate the hypotensive effect of clonidine. The findings of this study support the hypothesis and provide the first evidence that demonstrates an adverse influence of chronically consumed ethanol on the hypotensive response elicited by centrally acting drugs. These findings may have clinical relevance because they may explain in part the inadequate blood pressure control of treated hypertensive patients who simultaneously consume alcohol. The most significant findings of the present study are the following: (1) ethanol coadministration abolishes the hypotensive response elicited by clonidine in conscious SHR; (2) the adverse hemodynamic interaction cannot be simply explained by a counterbalancing (pressor) effect of ethanol because ethanol failed to increase the blood pressure of SHR; and (3) ethanol adversely influences the function of central structures involved in the hypotensive effect of clonidine.

Previous findings including our own have replicated the clinically reported pressor effect of long-term alcohol intake in normotensive rats.

Despite this limitation, it was important to use the SHR in the present study for two reasons. First, a short-term adverse hemodynamic interaction between ethanol and centrally acting drugs has been reported in SHR chronically fed ethanol.

A number of factors may explain the disparity between the blood pressure responses of SHR and age-matched normotensive rats. The substantial reduction in fluid intake that follows the addition of alcohol to the drinking water is considered an important factor because alcohol administered by gavage, to avoid the reduction in fluid intake, elicits a pressor response in alcohol-fed SHR. Despite this limitation, it was important to use the SHR in the present study for two reasons. First, a short-term adverse hemodynamic interaction between ethanol and centrally acting drugs has been reported in SHR. Second, clonidine added to the drinking water of SHR elicits the expected hypotensive response; clonidine lacks its hypotensive effect in conscious normotensive rats. It is also notable that the study was undertaken to address a clinically relevant problem that involves a potential interaction between alcohol and antihypertensive drugs in hypertensive individuals. To our knowledge, no such study has been reported.

Many reports (eg, References 11 and 12) have suggested that poor compliance with drug therapy plays a...
major part in the inadequate blood pressure control of treated hypertensive individuals who are regular alcohol users. However, the finding that such a problem also exists in hypertensive patients who have reported greater than 90% compliance with therapy\textsuperscript{13,15} has challenged this notion. The conclusion that concurrent alcohol consumption adversely influences the therapeutic benefit of antihypertensive therapy is further strengthened by the findings of a controlled crossover study.\textsuperscript{12} The findings of the present study support this view. However, unlike the clinical study, in which the effect of ethanol was investigated on the pooled hypotensive responses elicited by a variety of monotherapies and combined therapies,\textsuperscript{13} the present investigation focused on the interaction between ethanol and clonidine, a prototype of centrally acting drugs. The present findings extend our previous findings with clonidine\textsuperscript{1} and another centrally acting drug, guanabenz,\textsuperscript{2} in which acutely administered ethanol attenuated the hypotensive response elicited by these drugs in conscious SHR. It was not clear from these previous studies whether such an adverse hemodynamic interaction will manifest when ethanol and clonidine are administered on a long-term basis. This is important because the reported clinical problem pertains to a long-term difficulty in controlling the blood pressure of treated hypertensive patients who are regular alcohol users.\textsuperscript{10-13,15} The present findings provide the first experimental evidence for an adverse long-term hemodynamic interaction between ethanol and clonidine.

The mechanism by which ethanol abolishes the hypotensive response elicited by clonidine is not known. It may be argued that the interaction is an expected result of two directionally opposite hemodynamic responses elicited by clonidine and ethanol. It has been documented that clonidine acts within the central nervous system to inhibit sympathetic tone and consequently lowers blood pressure.\textsuperscript{7} On the other hand, many reports including our own have demonstrated a pressor effect of chronically consumed ethanol in humans and experimental animals.\textsuperscript{16-19,21-23} In our previous study, we showed that the pressor effect of ethanol was associated with sympathetic overactivity.\textsuperscript{23} It is notable, however, that the abolition of the hypotensive response elicited by clonidine cannot be attributed to a pressor effect of ethanol that might have nonspecifically counterbalanced the hypotensive response because chronically administered ethanol failed to increase the blood pressure of SHR. Nonetheless, it is important to note that ethanol-induced sympathetic overactivity has been reported in the absence of any change in blood pressure.\textsuperscript{4-22} Furthermore, the sympathoexcitatory effect of ethanol might be enhanced in the presence of a subnormal sympathetic activity, as is the case after treatment with clonidine and other centrally acting drugs.\textsuperscript{27} Our previous findings support this notion, showing that (1) ethanol attenuates hypotensive responses elicited by centrally mediated sympathoinhibition but not those associated with reflex increases in sympathetic activity,\textsuperscript{13,14} (2) ethanol reverses the decreases in plasma norepinephrine elicited by centrally acting drugs,\textsuperscript{2} and (3) the sympathoexcitatory action of ethanol is mediated centrally because it is blocked by the ganglion blocker hexamethonium.\textsuperscript{2} Evidence for the involvement of the sympathetic nervous system in the long-term hemodynamic interaction between ethanol and clonidine will be sought in future studies by measurement of plasma norepinephrine levels.

The daily amount of ethanol consumed by the SHR during weeks 4 through 13 was high and exceeded the amount of alcohol regularly consumed by human hypertensive individuals, except for heavy drinkers. Similarly, the clonidine dose used was much higher than clinically prescribed doses, given the fact that higher clonidine doses are associated with a high incidence of adverse effects.\textsuperscript{32} Neither treatment caused any mortality. However, it is possible that the adverse effects of both agents when administered concurrently were not tolerated by rats and may account for the 20% mortality in the group that received the combination. Selection of clonidine and ethanol doses was based on published reports on each agent. The clonidine dose used in another study\textsuperscript{24} elicited a lowering of blood pressure of 20 to 25 mm Hg, allowing adequate statistical comparison with the other groups. It will be interesting in future studies to explore whether the same interaction occurs when smaller doses of clonidine and a reduced amount of alcohol are used. The amount of ethanol provided to the SHR was similar to that consumed by normotensive rats in our previous studies\textsuperscript{20,22} and in others.\textsuperscript{31} In these previous studies, ethanol administered by the same paradigm used in the present study elicited a pressor response in normotensive rats.\textsuperscript{21-23} In contrast, and in agreement with the present finding, long-term ethanol administration elicited little change or a hypotensive response in SHR.\textsuperscript{28,29} The reasons for the contrasting effects of long-term ethanol administration on the blood pressure of SHR and normotensive rats are not known. It is likely, however, that SHR exhibit a greater sensitivity to ethanol compared with normotensive rats. Long-term ethanol administration led to a significant reduction in fluid intake and body weight of SHR in the present study. On the other hand, in normotensive rats, the same paradigm of ethanol feeding elicited small or no reduction in body weight and fluid intake.\textsuperscript{21-23} The drastic reduction in fluid intake that has been implicated in the dehydration associated with long-term ethanol administration to SHR\textsuperscript{29} may consequently lead to hypotension. If this is true, then the latter response, depending on its magnitude, is expected to at least offset the pressor effect of ethanol as in the present study or precipitate a hypotensive response as in other studies.\textsuperscript{28,29} In support of this notion is the finding that in the absence of any reduction in fluid intake when ethanol was administered by gavage, the ethanol-fed SHR exhibited a significantly higher blood pressure compared with controls.\textsuperscript{30} If this is the case, then the similar reduction in fluid intake of the group that received the combined treatment may have provided an underestimate of the blood pressure response of this group; ie, the blood pressure of the combined treatment group should have been higher than that obtained.

Results of the present study suggest that chronically administered ethanol adversely influences the function of the central nervous system structures involved in the hypotensive effect of clonidine. The findings demonstrate for the first time that ethanol-fed SHR exhibit a significantly smaller hypotensive response to intracisternally administered clonidine compared with control rats. Recent evidence suggests that clonidine lowers arterial pressure mainly by activating nonadrenergic imidazoline receptors in the rostral ventrolateral medulla and to a smaller extent
by activating α2-receptors. Interestingly, recent findings have demonstrated the ability of acutely administered ethanol to adversely influence the function of the neurons of the rostral ventrolateral medulla that modulate the baroreceptor heart rate response. Furthermore, our previous findings have demonstrated the selectivity of the adverse effect of ethanol on the hypotensive responses elicited by two centrally acting drugs, clonidine and guanabenz which are mixed agonists to the imidazoline/guanidinium and α2-receptors. It remains to be determined whether chronically administered ethanol impedes the function of either or both receptors.

In conclusion, long-term coadministration of ethanol abolishes the hypotensive response elicited by clonidine in SHR. This adverse hemodynamic interaction may explain in part the inadequate control of blood pressure of treated hypertensive individuals who continue to use alcohol. Other mechanisms that must also be operative and need to be considered are (1) the pressor effect of ethanol that is evident in humans but not in SHR and (2) poor adherence to the treatment program in heavy alcohol users. Whether a pharmacokinetic interaction may account in part for the ethanol-clonidine hemodynamic interaction is not known. Results of the present study show that blood ethanol concentration was similar in the presence and absence of clonidine. However, it remains to be determined whether ethanol coadministration influences the circulating levels of clonidine. Nonetheless, direct evidence presented in the present study demonstrates the ability of chronically administered ethanol to exert a pharmacodynamic effect that involves the central structures implicated in the hypotensive action of clonidine. Chronically administered ethanol significantly attenuated the hypotensive response elicited by centrally (acutely) administered clonidine in conscious unrestrained SHR. This finding suggests a potential interaction between ethanol and the central structures and receptors involved in the hypotensive effect of clonidine.

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