Acute Alcohol Administration Stimulates Baroreceptor Discharge in the Dog

Wei Wang, Marian Brändle, and Irving H. Zucker

It has been shown that alcohol administration causes baroreceptor reflex inhibition. The site of action of alcohol could reside anywhere within the baroreceptor reflex arc. Therefore, the goal of this study was to determine the effects of acute administration of alcohol on carotid sinus baroreceptor discharge characteristics. In pentobarbital-anesthetized dogs, the carotid sinus was isolated and perfused. Single unit baroreceptor discharge was recorded from the carotid sinus nerve along with carotid sinus pressure. Carotid sinus pressure–baroreceptor discharge and carotid sinus pressure–diameter curves were constructed. Perfusion of the carotid sinus with alcohol (100 mmol/L) significantly decreased the pressure threshold from 91.1±2.8 to 86.4±2.9 mm Hg (p<0.05) and increased the peak discharge rate from 45.8±3.4 to 52.8±3.6 spikes per second (p<0.01). The same phenomenon was seen during perfusion of the carotid sinus with acetaldehyde (2.5 mmol/L) but was not seen during perfusion with acetate (2.5 mmol/L). During perfusion of the carotid sinus with alcohol, the carotid sinus pressure–carotid sinus diameter relation did not change. The baroreceptor sensitization induced by alcohol is not an endothelium-dependent mechanism, because endothelial denudation did not block this alcohol-induced effect. Measurement of the duration of postexcitatory depression of carotid sinus baroreceptors, which is related to Na⁺,K⁺-ATPase activity, showed that perfusion of the carotid sinus with alcohol or acetaldehyde significantly reduced the duration of postexcitatory depression, indicating that the alcohol- and acetaldehyde-induced effect on baroreceptor discharge is most likely mediated by an inhibition of Na⁺,K⁺-ATPase. These data strongly suggest that the inhibition of the baroreceptor reflex after acute alcohol administration does not reside in the afferent limb of the baroreceptor reflex arc.

Key Words • pressoreceptors • alcohol, ethyl • acetaldehyde • adenosine triphosphatase, sodium, potassium

I t is well known that chronic and acute ingestion of alcohol is associated with hypertension and other cardiovascular diseases. Unfortunately, the mechanisms involved in alcohol-induced hypertension are not well understood. It is well accepted that the baroreceptor reflex plays an important role in the control of blood pressure. Recent studies have shown that chronic and acute alcohol administration causes baroreceptor reflex inhibition. This alcohol-induced baroreceptor reflex depression may reside in any part of the baroreceptor reflex arc (baroreceptors, central nervous system, efferent limb, or target organ). It has been reported in a morphometric study that the fiber density of the carotid sinus nerve, which carries baroreceptor and chemoreceptor fibers, is significantly decreased in patients who succumbed to the sequelae of chronic alcoholism. To our knowledge, no functional study has investigated the effects of alcohol on baroreceptor discharge characteristics. Because ethanol has potent effects on biological membranes, the function of the baroreceptors may be significantly impaired by ethanol or its metabolites. Therefore, the aims of the present study were 1) to determine the effects of acute carotid sinus administration of alcohol and its major metabolites on carotid sinus baroreceptor discharge characteristics, 2) to determine if the effects of alcohol are mediated by an endothelium-dependent mechanism, and 3) to determine if the effects of alcohol and its major metabolites on baroreceptor function are mediated by changes in Na⁺,K⁺-ATPase activity.

The data obtained in this study suggest that acute administration of alcohol and acetaldehyde but not acetate can stimulate carotid sinus baroreceptors and that this effect is not endothelium dependent and may be mediated by inhibition of Na⁺,K⁺-ATPase activity.

Methods

Twenty-six normotensive, adult mongrel dogs of either sex weighing 19–28 kg were used in the present study. All animals were fed and housed according to institutional guidelines at the University of Nebraska. These studies were approved by the University of Nebraska Medical Center Animal Review Committee. Each dog was anesthetized with sodium pentobarbital (30 mg/kg i.v.) and intubated. A femoral artery was catheterized for acquisition of blood samples and mea-
suture placed through the adventitia. The diameter was placed on the medial and lateral aspects of the carotid junction with the glossopharyngeal nerve trunk. The was amplified with a Grass DC preamplifier (model D, A.R. Vetter Co., Rebersburg, Pa.) and on an electrostatic strip-chart recorder (model ES recorder (model ES 1000, Gould Instruments, Glen Burnie, Md.)) connected to a neuronal spike analyzer (model N750, Mentor, Minneapolis, Minn.). A window discriminator was set so that impulses from only one fiber were discriminated even if activity from more than one fiber was recorded. The discriminator pulses thus corresponded only to the desired single unit baroreceptor discharge. The raw nerve activity, discriminated pulses, and CSP were recorded on an FM tape recorder (model D, A.R. Vetter Co., Rebersburg, Pa.) and on an electrostatic strip-chart recorder (model ES 1000, Gould Instruments, Glen Burnie, Md.).

Carotid Sinus Diameter

A pair of 2-mm piezoelectric crystals (5 MHz) were placed on the medial and lateral aspects of the carotid bifurcation. The crystals were secured with one 5-0 suture placed through the adventitia. The diameter was measured with a sonomicrometer dimension system (Triton Technology, Inc., San Diego, Calif.).

Construction of Carotid Sinus Pressure–Diameter and Discharge Curves

For the pressure–discharge curve, pressure threshold was measured by increasing CSP with a slow ramp (2–3 mm Hg/sec) until discharge was initiated; thereafter, pressure was changed in the isolated carotid sinus up to 250 mm Hg in static steps of 25 mm Hg. Each pressure step was held for approximately 15 seconds and the pressure, discharge, and diameter data were averaged by computer over the last 5 seconds of each step. Each curve took approximately 2.5 minutes to complete. Flow was maintained through the carotid sinus during pressurization. For the pressure–diameter curve, a 25 mm Hg step was used from 25 to 250 mm Hg, the data taken approximately 10 seconds after each step was initiated.

Removal of Endothelial Cells

A chemical removal technique was used in this study,2324 which entails perfusion of the carotid sinus with 0.5 mg/mL of saponin (Fisher Scientific Co., Fairlawn, N.J.) in oxygenated Krebs-Henseleit solution for approximately 3 minutes. In our previous study,25 both morphological and functional data showed that this technique successfully removed the endothelial cells.

Measurement of Postexcitatory Depression of Baroreceptors

Postexcitatory depression (PED) was assessed by plotting the amplitude and duration of several pressure steps against the duration of the PED. CSP was kept at 100 mm Hg for at least 10 minutes before construction of each pressure step–duration of PED or duration of pressure step–duration of PED relation. During the generation of the amplitude of pressure step versus duration of PED relation, the CSP was elevated to 120 mm Hg (superthreshold level) and held until a steady-state discharge rate was obtained. Thereafter, the CSP was sharply increased to a higher level (140, 160, 180, or 200 mm Hg) by turning a stopcock that was connected to a second pressure reservoir set to the desired step pressure. The pressure step was held for 4 seconds before being released. The period of discharge silence after removal of the pressure step was measured. The period of silence was defined as the duration between the last spike recorded before the pressure step was released and return of the first spikes after the pressure had returned to control (120 mm Hg). During construction of the duration of pressure step versus duration of PED relation, the basal level of CSP was kept at 120 mm Hg. The pressure step was set at 200 mm Hg and held between 1 and 10 seconds before being returned to 120 mm Hg.

Experimental Protocols

Control CSP–single unit baroreceptor discharge and CSP–carotid sinus diameter curves were constructed during perfusion with Krebs-Henseleit solution. A second set of CSP–discharge and CSP–diameter curves was constructed during perfusion with alcohol at doses between 20 and 100 mmol/L for 5 minutes. The effects of acute administration of alcohol on baroreceptor...
control state to 76 mm Hg during alcohol perfusion, and the peak discharge rate was significantly increased from 50 to 60 spikes per second. Figure 2 shows average data of the effects of acute administration of alcohol on baroreceptor discharge characteristics. The threshold was significantly decreased from 91.1±2.8 to 86.4±2.9 mm Hg (p<0.05), and the peak discharge rate was significantly increased from 45.8±3.4 to 52.8±3.6 spikes per second (p<0.01) after administration of 100 mmol/L alcohol. The effect of acute administration of alcohol on baroreceptor discharge sensitivity occurred within 5 minutes and was reversed after reperfusion of the carotid sinus with normal Krebs-Henseleit solution. This alcohol-induced baroreceptor sensitization exhibited a dose-dependent relation (Figure 3). The data obtained from this experiment suggest that acute administration of alcohol can increase carotid sinus baroreceptor discharge sensitivity.

**Results**

**Effects of Acute Administration of Alcohol on Carotid Sinus Baroreceptor Discharge**

In 16 single baroreceptor preparations, alcohol was infused into the isolated, Krebs-Henseleit-perfused carotid sinus. Figure 1 shows a representative recording from one of these experiments. The left panel in Figure 1 shows a single unit baroreceptor discharge response to increases in CSP in the control state (without alcohol), and the right panel shows its responses to increases in CSP after perfusion of alcohol (100 mmol/L) for 5 minutes. As seen in this figure, the threshold pressure was significantly decreased from 90 mm Hg in the control state to 76 mm Hg during alcohol perfusion, and the peak discharge rate was significantly increased from 50 to 60 spikes per second. Figure 2 shows average data of the effects of acute administration of alcohol on baroreceptor discharge characteristics. The threshold was significantly decreased from 91.1±2.8 to 86.4±2.9 mm Hg (p<0.05), and the peak discharge rate was significantly increased from 45.8±3.4 to 52.8±3.6 spikes per second (p<0.01) after administration of 100 mmol/L alcohol. The effect of acute administration of alcohol on baroreceptor discharge sensitivity occurred within 5 minutes and was reversed after reperfusion of the carotid sinus with normal Krebs-Henseleit solution. This alcohol-induced baroreceptor sensitization exhibited a dose-dependent relation (Figure 3). The data obtained from this experiment suggest that acute administration of alcohol can increase carotid sinus baroreceptor discharge sensitivity.

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Effects of Acetaldehyde and Acetate on Baroreceptor Discharge

Perfusion of the carotid sinus with 2.5 mmol/L of acetaldehyde (n=8) significantly decreased threshold from 95.1±3.4 to 70±6.9 mm Hg (p<0.01) and increased peak discharge rate from 45.6±4.0 to 74.1±10.7 spikes per second (p<0.01) (left panel, Figure 4). However, perfusion of the carotid sinus with 2.5 mmol/L acetate (n=5) had no effect on the CSP-discharge curve (right panel, Figure 4).

Effect of Alcohol on Carotid Diameter

In 10 carotid diameter recordings, the effect of alcohol on carotid diameter was investigated. Figure 5 shows the average data. As can be seen, alcohol had no effect on carotid diameter or its compliance (the slope of the CSP–diameter curve).

Effects of Alcohol on Baroreceptor Discharge After Removal of Endothelial Cells

In six single baroreceptor preparations, we determined if the effects of alcohol on baroreceptor discharge was endothelium dependent. Removal of the endothelium by perfusion of the carotid sinus with saponin (0.5 mg/mL for 3 minutes) had no effect on baroreceptor discharge sensitivity (Figure 6). Perfusion of the carotid sinus with alcohol in the endothelium-denuded vessel still significantly decreased threshold from 98.0±5.9 to 91.0±4.8 mm Hg (p<0.01) and increased peak discharge rate from 34.7±3.3 to 45.5±5.6 spikes per second (p<0.01).

Effects of Alcohol and Its Metabolites on Postexcitatory Depression

In 12 single baroreceptor preparations, the duration of PED was measured before and after administration of alcohol. Figure 7 shows a representative recording from one of these experiments. As can be seen in this figure, the duration of PED was shortened during alcohol infusion. The mean data from these experiments are shown in Figure 8. Data are shown for both amplitude of the pressure step at a constant duration (top panel) and duration of the pressure step at a constant amplitude (bottom panel). During the control period, PED ranged from 1.8±0.6 to 4.2±0.9 seconds as the duration of the pressure steps was varied and from 1.8±0.6 to 2.8±0.8 seconds as the amplitude of the pressure steps was varied. During alcohol perfusion, there was a significant shortening of PED for both the duration and amplitude of the pressure step applications (from 0.6±0.3 to 1.4±0.6 seconds for change in the duration of the pressure steps and from 0.6±0.3 to 2.4±0.8 seconds for change in the amplitude of the pressure steps).

In another eight single baroreceptor preparations, the effects of acetaldehyde on PED were investigated. Similar to the effects of alcohol, acetaldehyde significantly reduced the duration of PED to changes in amplitude of the pressure step and duration of the pressure step (Figure 9). However, perfusion of the...
Acute and chronic administration of alcohol has been shown to result in a variety of cardiovascular responses, depending on the tissue, the route of administration, and the species studied. Considerable epidemiological evidence suggests a positive relation between alcohol consumption and arterial blood pressure. Indeed, it has recently been shown that the effect of alcohol consumption on blood pressure is a rapidly reversible phenomenon. It has been reported that a relation between alcohol consumption and blood pressure is independent of age, sex, obesity, race, or cigarette smoking. This is not to say that these cofactors may not potentiate or contribute to the severity of the alcohol-induced hypertension.

Unfortunately, no study has clearly identified the mechanism or mechanisms by which alcohol elevates blood pressure. It is widely accepted that the arterial baroreceptor reflex plays an important role in the control of blood pressure. On the other hand, the baroreceptor reflex control of heart rate is known to be depressed in human and experimental hypertension. A series of studies by Abdel-Rahman, Zhang, and Woolles have shown that acute or chronic administration of alcohol impaired the baroreceptor reflex control of heart rate in rats and in normotensive humans. The fact that there was a positive correlation between blood alcohol concentration and the degree of baroreceptor reflex impairment suggested that these effects were alcohol mediated. It is apparent that the site of action of alcohol could be anywhere within the baroreceptor reflex arc: at the arterial baroreceptors, which are located in the carotid sinus and aortic arch; in the central nervous system; at the efferent limb of the reflex arc; or at the target organ. In one study from this group, it was shown that the baroreceptor reflex control of sympathetic efferent discharge was not impaired by acute alcohol administration, whereas the baroreceptor reflex control of heart rate was, indicating that alcohol had a differential effect on these baroreceptor reflex-controlled variables. A morphometric study by Tamura et al has shown that nerve fiber density in the carotid sinus was significantly decreased.

**Discussion**

Acute and chronic administration of alcohol has been shown to result in a variety of cardiovascular responses, depending on the tissue, the route of administration, and the species studied. Considerable epidemiological evidence suggests a positive relation between alcohol consumption and arterial blood pressure. Indeed, it has recently been shown that the effect of alcohol consumption on blood pressure is a rapidly reversible phenomenon. It has been reported that a relation between alcohol consumption and blood pressure is independent of age, sex, obesity, race, or cigarette smoking. This is not to say that these cofactors may not potentiate or contribute to the severity of the alcohol-induced hypertension.

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**Figure 7.** Representative recordings of post-excitatory depression of baroreceptor before (top panel) and during (bottom panel) perfusion with alcohol (100 mmol/L). Amplitude of each step was 80 mm Hg, and pulse duration was varied. Alcohol reduced the period of silence for each pulse. CSP, carotid sinus pressure.
in patients with chronic alcoholism. There has been no functional study to investigate the effects of acute administration of alcohol on baroreceptor discharge characteristics. In the present study, perfusion of the carotid sinus with alcohol significantly decreased threshold and increased peak discharge rate, indicating acute alcohol administration sensitizes baroreceptor activity. This alcohol-induced baroreceptor sensitization occurred within several minutes and could be rapidly reversed by reperfusion with normal Krebs-Henseleit solution. The dose of alcohol used in this study ranged from 20 to 100 mmol/L. These levels have been reported to occur in humans. Although 100 mmol/L may be higher than that seen in intoxicated humans, there was a significant sensitization of carotid sinus baroreceptors at doses as low as 20 mmol/L. Although 100 mmol/L was used in many of the present experiments, it must be kept in mind that we used a flow-through system and did not recirculate the perfusate. It is therefore difficult to equate the doses used here with the level of alcohol that may occur in humans ingesting variable amounts of alcohol.

The major pathway for the disposition of alcohol is its metabolism to acetaldehyde via alcohol dehydrogenase. Acetaldehyde is further oxidized to acetate, which is then converted to CO₂ via the citric acid cycle. In the present study, perfusion of the carotid sinus with acetaldehyde (2.5 mmol/L) significantly decreased threshold and increased peak discharge; however, perfusion of the carotid sinus with the same concentration of acetate had no effect on baroreceptor discharge. These data indicate that alcohol and its major metabolite, acetaldehyde, may play an important role in sensitizing baroreceptor endings.

What are the mechanisms involved in this alcohol-induced effect? Baroreceptors are stretch receptors. Any agent that can change vessel compliance may affect baroreceptor discharge sensitivity. It has been reported that alcohol acts as a vasodilator in skeletal muscle and splanchnic microvessels; however, a small but convincing body of literature exists that shows a role for alcohol in mediating constrictor responses in both large and

**FIGURE 8.** Plots of mean data show effects of alcohol (100 mmol/L) on duration of carotid sinus baroreceptor postexcitatory depression (PED) (n=12). Top panel: Duration of PED vs. amplitude of pressure step; bottom panel: duration of PED vs. duration of pressure step. Infusion of alcohol uniformly reduced duration of PED. *p<0.05, control vs. alcohol.

**FIGURE 9.** Plots of mean data show effects of acetaldehyde (2.5 mmol/L) on duration of postexcitatory depression (PED) (n=8). Top panel: Duration of PED vs. amplitude of pressure step; bottom panel: duration of PED vs. duration of pressure step. *p<0.05, control vs. acetaldehyde.

**FIGURE 10.** Plots of mean data show effects of acetate (2.5 mmol/L) on duration of carotid sinus baroreceptor postexcitatory depression (PED) (n=6). Top panel: Duration of PED vs. amplitude of pressure step; bottom panel: duration of PED vs. duration of pressure step.
small vessels.32 Recent studies indicate that the effect of alcohol on vessel smooth muscle is modulated by an endothelium-dependent mechanism.33–35 In the present study, the CSP–carotid diameter relation did not change after alcohol (Figure 6), indicating that alcohol-induced baroreceptor sensitization is not mediated by change in vessel compliance. In addition, removal of the endothelial cells with saponin did not have any effect on baseline baroreceptor function (Figure 7) or on acute alcohol-induced baroreceptor sensitization. These data suggest that the effects of acute administration of alcohol on baroreceptor discharge is not endothelium dependent.

It has been reported, with the use of synaptic plasma membranes isolated from cerebral cortex of Sprague-Dawley rats, that alcohol can inhibit Na⁺,K⁺-ATPase.36 It has also been shown that high concentrations of cardiac glycosides, which block Na⁺,K⁺-ATPase, can augment baroreceptor discharge sensitivity.37 The PED is widely accepted to be related to increased Na⁺,K⁺-ATPase activity, because ouabain can abolish PED.38 In the present study, perfusion of the carotid sinus with alcohol or acetaldehyde significantly reduced the duration of PED to both changes in the amplitude of pressure steps and changes in the duration of pressure steps. However, perfusion of the carotid sinus with acetate had no effect on PED. Therefore, alcohol- or acetaldehyde-induced baroreceptor sensitization may be mediated by inhibition of Na⁺,K⁺-ATPase in the carotid sinus baroreceptor membrane. Both of these substances are highly lipid soluble and penetrate membranes with ease.

In summary, acute administration of alcohol and acetaldehyde but not acetate increased carotid sinus baroreceptor discharge sensitivity and peak discharge. This effect is not mediated by a dilatation of the carotid sinus and is not an endothelium-dependent mechanism. In addition, both alcohol and acetaldehyde but not acetate reduced the duration of PED. These data are consistent with a direct effect of alcohol and acetaldehyde on baroreceptor endings. The mechanism of this effect may be related to inhibition of Na⁺,K⁺-ATPase activity, because the duration of the PED was shortened. These data strongly suggest that the inhibition of the baroreceptor reflex after acute alcohol administration does not reside in the afferent limb of the baroreceptor reflex arc.

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