Title: Suppression of alcohol-induced hypertension by dexamethasone.

Authors: Randin D, Vollenweider P, Tappy L, Jéquier E, Nicod P, Scherrer U

Journal: The New England journal of medicine

Year: 1995 Jun 29

Volume: 332

Issue: 26

Pages: 1733-7

DOI: 10.1056/NEJM199506293322601

The New England
Journal of Medicine

Volume 332 JUNE 29, 1995 Number 26

SUPPRESSION OF ALCOHOL-INDUCED HYPERTENSION BY DEXAMETHASONE

DENIS RANDIN, M.D., PETER VOLLENWEIDER, M.D., LUC TAPPY, M.D., ERIC JÉQUIER, M.D., PASCAL NICOD, M.D., AND URS SCHERRER, M.D.

Abstract *Background.* Alcohol consumption is associated with an increased incidence of hypertension and stroke, but the triggering mechanisms are unclear. In animals, alcohol causes activation of the sympathetic nervous system and also stimulates the release of corticotropin-releasing hormone (CRH), which has sympathoexcitatory effects when administered centrally.

Methods. To determine whether alcohol evokes sympathetic activation and whether such activation is attenuated by the inhibition of CRH release, we measured blood pressure, heart rate, and sympathetic-nerve action potentials (using intraneural microelectrodes) in nine normal subjects before and during an intravenous infusion of alcohol (0.5 g per kilogram of body weight over a period of 45 minutes) and for 75 minutes after the infusion. Each subject received two infusions, one after the administration of dexamethasone (2 mg per day) and one after the administration of a placebo for 48 hours.

Results. The infusion of alcohol alone evoked a marked ($P<0.001$) and progressive increase in the mean ($\pm$SD) rate of sympathetic discharge, from 16 ± 3 bursts per minute at base line to 30 ± 8 bursts per minute at the end of the two-hour period. This sympathetic activation was accompanied during the second hour by an increase in mean arterial pressure of 10 ± 5 mm Hg ($P<0.001$). After the administration of dexamethasone, the alcohol infusion had no detectable sympathetic effect. The dexamethasone-induced suppression of sympathetic activation was associated with a decrease in mean arterial pressure of 7 ± 6 mm Hg ($P<0.001$) during the alcohol infusion and with suppression of the pressor effect during the second hour.

Conclusions. Alcohol induces pressor effects by sympathetic activation that appear to be centrally mediated. It is possible that these alcohol-induced hemodynamic and sympathetic actions could participate in triggering cardiovascular events. (N Engl J Med 1995;332:1733-7.)

ALCOHOL consumption is a risk factor for stroke and is associated with a higher-than-expected incidence of hypertension.[1-6] The underlying mechanism relating heavy alcohol consumption to cardiovascular events is unclear.[7,8] One potential candidate is the sympathetic nervous system. The results of plasma catecholamine measurements after the short-term ingestion of alcohol in humans are conflicting,[5,7,8] but direct recordings of sympathetic-nerve activity suggest that short-term alcohol ingestion in humans and both short- and long-term administration of ethanol in rats stimulate sympathetic-nerve discharge.[9-11] Moreover, in rats the alcohol-induced increases in blood pressure and sympathetic activity are centrally mediated.[12]

Alcohol stimulates the secretion of corticotropin-releasing hormone (CRH) in rats,[13,14] an effect that could explain why regular alcohol consumption stimulates cortisol secretion.[15] In rats, the intracerebroventricular administration of CRH increases blood pressure[16] and stimulates sympathetic activity,[17] and the inhibition of CRH release by dexamethasone attenuates stress-induced sympathetic activation.[18] In humans dexamethasone, possibly by its inhibitory effect on CRH release, inhibits insulin-induced sympathetic activation.[19]

We attempted to determine whether the short-term intravenous administration of alcohol stimulates sympathetic-nerve activity and, if so, whether the administration of dexamethasone attenuates this sympathetic activation in normal humans. We therefore measured sympathetic-nerve activity and hemodynamic changes during two infusions of alcohol, one after the administration of dexamethasone and the other after the administration of placebo. To gain further insight into the relation between the sympathetic and vascular actions of alcohol, we tested the effects of an alpha-adrenergic–receptor blockade on the hemodynamic response to an alcohol infusion.

METHODS

Subjects

We studied nine normal subjects (three women and six men; mean [$\pm$SD] weight, 67 ± 10 kg; height, 175 ± 8 cm; body-mass index, 21.3 ± 1.7; and age, 27 ± 5 years). (Body-mass index was calculated as

From the Department of Internal Medicine B, Centre Hospitalier Universitaire Vaudois (D.R., P.N., U.S.); and the Institute of Physiology, University of Lausanne (P.V., L.T., E.J.) — both in Lausanne, Switzerland. Address reprint requests to Dr. Scherrer at the Department of Internal Medicine B, BH 10.642, CHUV, CH-1011 Lausanne, Switzerland.

Supported by a grant (32-36280.92) from the Swiss National Science Foundation and by Nestec, Vevey, Switzerland; the International Olympic Committee; and the Max Cloëtta Foundation.

Presented in part at the 47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research, San Francisco, September 28–October 1, 1993.

the weight in kilograms divided by the square of the height in meters.) All the subjects were normotensive, were taking no medications, and had no evidence of metabolic or cardiovascular disease. Their customary alcohol consumption was less than 50 g per week. All the studies were performed in the morning after an overnight fast over a period of one to six weeks. The subjects were asked to abstain from alcohol, caffeine, and tobacco for at least 24 hours before each study. The experimental protocol was approved by the Institutional Review Board on Human Investigation, and all subjects provided written informed consent.

General Procedures

The subjects were studied in the supine position. Data on heart rate (monitored with an electrocardiograph), respiratory excursions (pneumobelt), blood pressure (Finapres blood-pressure monitor [Ohmeda, Englewood, Colo.]),[20] blood flow in the calf (venous-occlusion plethysmography),[20] and sympathetic-nerve activity in efferent nerves were recorded continuously on an electrostatic recorder and a tape recorder (R71, TEAC, Tokyo, Japan). Respiratory excursions were monitored to detect the inadvertent performance of a Valsalva maneuver or prolonged expiration, since these respiratory maneuvers can stimulate sympathetic outflow.[20] Intravenous catheters were inserted in a right and a left antecubital vein, one for the alcohol infusion and the other for blood sampling.

Recordings of Sympathetic-Nerve Activity

Postganglionic sympathetic-nerve activity was recorded with unipolar tungsten microelectrodes inserted selectively into muscle–nerve fasciculi of the peroneal nerve posterior to the fibular head by the microneurographic technique of Vallbo et al.[21] The neural signals were amplified 20,000 to 50,000 times, filtered (band width, 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 second) to obtain a display of the mean voltage of sympathetic activity. A recording of sympathetic activity was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each study, we documented that we were recording the sympathetic outflow to skeletal muscle by demonstrating that the neural activity did not respond to arousal stimuli (a loud noise) or a pinch of the skin but showed a characteristically biphasic response to the Valsalva maneuver.[22]

For analysis, printed filtered and mean-voltage neurograms were inspected visually to identify bursts of sympathetic-nerve discharge. The recordings were all analyzed by the same observer, who was unaware of whether the subject had received dexamethasone or placebo before the study. The intraobserver and interobserver coefficients of variation of the mean in identifying bursts were less than 6 percent and less than 9 percent, respectively.[20] Nerve traffic was expressed both as the number of bursts per minute, an index of the frequency of the activity, and as the number of bursts per minute times the mean amplitude of the bursts, an index of integrated (total) activity. For quantitative analysis, the results were normalized by transcribing the nerve recordings from FM tape to hard copy in such a way that mean burst amplitudes were comparable in all subjects.

Measurement of Blood Flow in Muscle

While recording the sympathetic-nerve outflow to the calf muscles in one leg, we simultaneously measured blood flow in the calf of the contralateral leg by venous-occlusion plethysmography, using mercury-in-Silastic strain gauges.[20] The calf was elevated 10 to 15 cm above the level of the right atrium to collapse the veins. The circulation to the foot was arrested by inflating a cuff around the ankle during each determination of blood flow; determinations were made at 15-second intervals over a 5-minute period.

Analytic Methods

Plasma alcohol concentrations were measured enzymatically (Alcool PAP, Biomérieux, Mercy l'Etoile, France). Plasma norepinephrine was measured by high-performance liquid chromatography,[20] and plasma insulin and cortisol by radioimmunoassay (Gamma-BCT Cortisol IDS, Boldon, United Kingdom). All samples from the same subject were analyzed at the same time in each assay.

Experimental Protocols

Alcohol Infusion after the Administration of Dexamethasone and Placebo

All nine subjects received in randomized, double-blind sequence either dexamethasone (2 mg per day in four divided doses) or identical placebo pills for 48 hours before each of two alcohol infusions. The last dose of dexamethasone or placebo was administered on the morning of the test. After base-line measurements for 30 minutes, alcohol (ethanol, 0.5 g per kilogram of body weight) diluted in normal saline to make a 10 percent solution was infused over a 45-minute period. Sympathetic-nerve activity and hemodynamic measurements were recorded for 5 minutes of each 15-minute period during the 30-minute base-line period, the 45 minutes of the alcohol infusion, and the 75 minutes after the infusion. Immediately thereafter, in six subjects, we used baroreceptor deactivation evoked by the Valsalva maneuver[19] and stimulation of cutaneous afferent nerves by a two-minute immersion of the hand in ice water[19] (the cold pressor test) to examine the effects of dexamethasone on the responses to stimuli of sympathetic discharge other than alcohol. Blood samples were collected at base line and 15, 30, 45, 60, 90, and 120 minutes after the start of the alcohol infusion for analysis of plasma concentrations of alcohol and hormones.

Effects of Alpha-Adrenergic Blockade (Phentolamine Infusion) on Hemodynamic Responses to Alcohol Infusion

We assessed the effects of alpha-adrenergic blockade on hemodynamic responses to alcohol infusion. The purpose of this part of the study was to determine whether the dexamethasone-induced attenuation of the alcohol-induced pressor response was causally related to the attenuation of alcohol-induced sympathetic activation. Five of the nine subjects participated in this test. After base-line measurements for 30 minutes, phentolamine was administered as a primed infusion (70 μg per kilogram given over a 5-minute period) and then as a continuous infusion (7 μg per kilogram per minute) for 55 minutes, after which alcohol (at the dose used in the first part of the study) and phentolamine (7 μg per kilogram per minute) were infused together for 45 minutes. After the cessation of the alcohol infusion, phentolamine was infused for another 75 minutes at the same dose. Hemodynamic measurements were recorded for 5 minutes during each 15-minute period of the 30-minute base-line period and of the 3 hours of the phentolamine infusion.

The efficacy of the alpha-adrenergic blockade was then assessed by examining the pressor response and the vascular-resistance response in the calf evoked by immersing the subject's hand in ice water for two minutes. The mean ($\pm$SD) arterial pressure increased by 25$\pm$9 mm Hg and the vascular resistance in the calf increased by 17$\pm$11 units before the phentolamine infusion, but the mean arterial pressure increased by only 13$\pm$4 mm Hg and the vascular resistance decreased by 5$\pm$14 units during the infusion.

Effects of a Bolus Dose of Dexamethasone on Sympathetic Activity and Arterial Pressure

We also determined the effects of the administration of a bolus dose of dexamethasone alone (in the absence of alcohol) on sympathetic-nerve traffic and arterial pressure. Five other normal subjects (four women and one man; weight, 62$\pm$8 kg; height, 169$\pm$7 cm; body-mass index, 22.0$\pm$1.6; and age, 27$\pm$6 years) participated. After base-line measurements for 30 minutes, 2 mg of dexamethasone was administered intravenously as a bolus dose, followed by an infusion of saline at the same rate and for the same duration as the infusion of alcohol in the first part of the study. Nerve traffic and arterial pressure were measured for two hours after the dexamethasone administration.

Statistical Analysis

Mean arterial pressure was calculated as diastolic blood pressure plus one third of the pulse pressure. Vascular resistance in the calf

was determined as the mean arterial pressure in millimeters of mercury divided by the blood flow in milliliters per minute per 100 milliliters of tissue; it was expressed in units.

The measurements of sympathetic-nerve activity, blood flow in the calf, blood pressure, and heart rate that were collected for 5 of every 15 minutes were averaged to a single value.

The statistical analysis was performed with an analysis of variance with repeated measures and paired two-tailed t-tests. Unless otherwise indicated, data are given as means ±SD. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Responses to the Alcohol Infusion after Dexamethasone and Placebo

The base-line values for sympathetic-nerve discharge, plasma norepinephrine concentration, vascular resistance in the calf, and blood pressure were not altered by the administration of dexamethasone. Compliance with the administration of dexamethasone was documented by the presence of plasma cortisol concentrations markedly lower than those measured after the administration of placebo (2.1±2.7 vs. 12.3±5.4 μg per deciliter [57±74 vs. 339±149 nmol per liter], P<0.001). The increases in plasma alcohol concentrations were similar under both experimental conditions (Table 1). Base-line plasma insulin concentrations were higher (P=0.004) after dexamethasone than after placebo. During the alcohol infusion, the mean plasma insulin concentration increased slightly, albeit significantly (P=0.01), both after placebo (from 6.6±2.9 to 8.2±2.4 μU per milliliter [40±17 to 49±14 pmol per liter] at 120 minutes) and after dexamethasone (from 11.2±4.1 to 13.5±6.6 μU per milliliter [67±25 to 81±40 pmol per liter]).

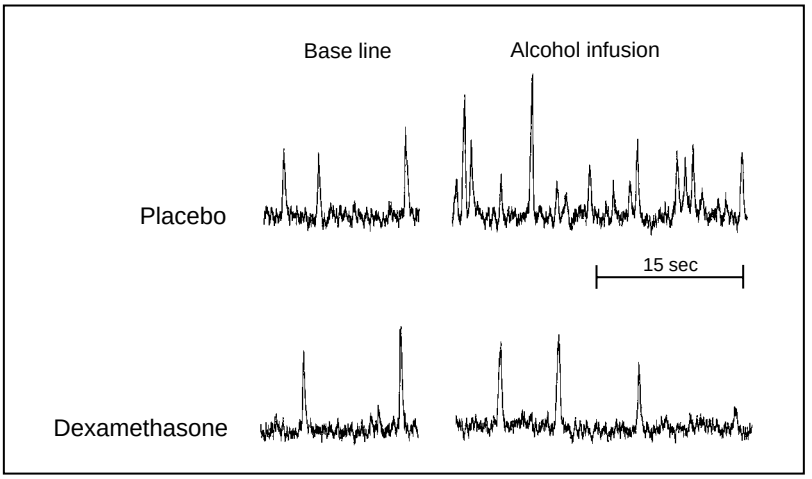

Figure 1. Representative Recordings of Sympathetic-Nerve Activity in a Normal Subject before and 120 Minutes after the Start of the Alcohol Infusion.
The infusions were given after the administration of placebo and dexamethasone. Each peak represents a spontaneous burst of sympathetic-nerve discharge.

After the administration of placebo, the alcohol infusion evoked marked, roughly linear increases in sympathetic-nerve activity (Fig. 1 and 2 and Table 1); at the end of the two-hour study period, the frequency of sympathetic-nerve bursts had increased by 97±54 percent and total activity by 127±84 percent (P<0.001). During the second hour, this progressive stimulation of sympathetic-nerve discharge was accompanied by an increase of 10±5 mm Hg (P<0.001) in mean arterial pressure (Fig. 2 and Table 1). The alcohol-induced increases in sympathetic-nerve discharge in skeletal muscle were reflected by significant increases in plasma norepinephrine concentrations. In contrast, the infusion of alcohol after the administration of dexamethasone had no detectable effect on sympathetic-nerve discharge (or on plasma norepinephrine concentrations). The lack of sympathetic activation was associated with a decrease of 7±6

Table 1. Responses to Alcohol Infusions Given after the Administration of Placebo or Dexamethasone for 48 Hours in Normal Subjects.*

VARIABLE	ALCOHOL INFUSION AFTER PLACEBO					ALCOHOL INFUSION AFTER DEXAMETHASONE				
	BASE LINE	AFTER 60 MIN	P VALUE	AFTER 120 MIN	P VALUE	BASE LINE	AFTER 60 MIN	P VALUE	AFTER 120 MIN	P VALUE
Sympathetic-nerve activity										
Bursts/min	16±3	22±5	<0.001	30±8	<0.001	16±5	17±5†	NS	17±5‡	NS
Units§	234±40	379±100	0.003	520±187	<0.001	246±67	252±66¶	NS	275±86‖	NS
Mean arterial pressure (mm Hg)	90±5	92±7	NS	100±8	<0.001	90±5	85±8**	0.003	89±7‡	NS
Heart rate (beats/min)	65±7	72±8	0.005	73±9	<0.001	62±6	70±5	<0.001	72±7	<0.001
Vascular resistance in the calf (units)	55±16	56±13	NS	55±17	NS	56±16	51±15	0.004	48±14	<0.001
Plasma norepinephrine (pg/ml)	182±42	231±79	0.007	237±77	0.003	153±29	164±42	NS	167±52††	NS
Plasma alcohol (mg/dl)	0±0	63±8	<0.001	45±7	<0.001	0±0	62±6	<0.001	42±5	<0.001

*Values are means ±SD for nine subjects except in the case of plasma norepinephrine (n=6). Alcohol (0.5 g per kilogram) was infused for 45 minutes. The P values are for the comparisons with the base-line values. To convert values for plasma norepinephrine to nanomoles per liter, multiply by 0.0059; to convert values for plasma alcohol to millimoles per liter, multiply by 0.22. NS denotes not significant.

†P=0.04 for the comparison with alcohol infusion after placebo.

‡P=0.003 for the comparison with alcohol infusion after placebo.

§Units of sympathetic-nerve activity are calculated as the number of bursts per minute times the mean amplitude of the bursts.

¶P=0.01 for the comparison with alcohol infusion after placebo.

‖P=0.007 for the comparison with alcohol infusion after placebo.

**P=0.002 for the comparison with alcohol infusion after placebo.

††P=0.02 for the comparison with alcohol infusion after placebo.

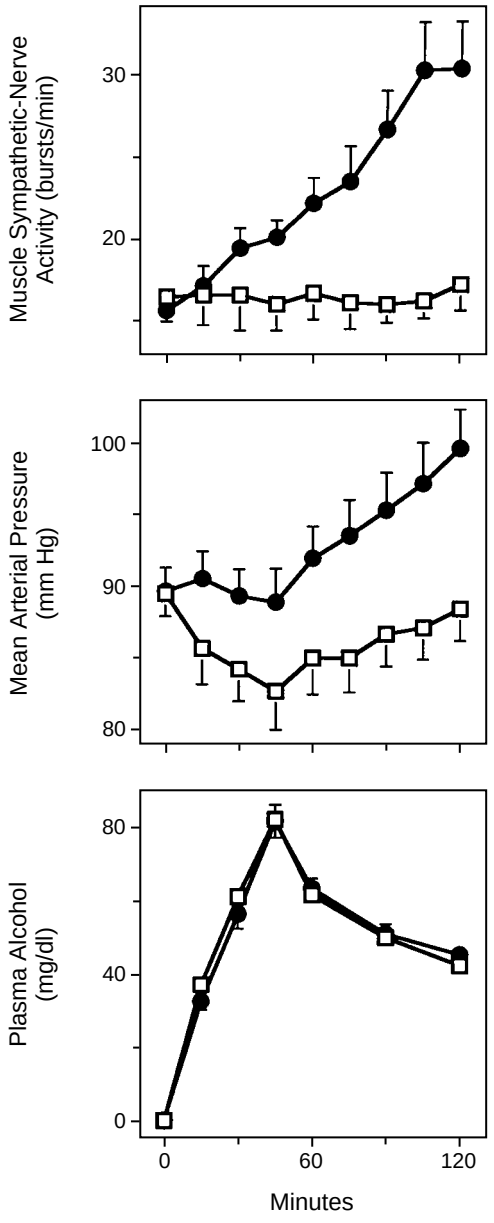

Figure 2. Mean (±SE) Effects of an Infusion of Alcohol in Nine Normal Subjects after the Administration of Placebo (●) or Dexamethasone (□).

The alcohol-induced sympathetic and pressor effects were abolished after the administration of dexamethasone ($P<0.001$ for the comparison between placebo and dexamethasone). To convert values for plasma alcohol to millimoles per liter, multiply by 0.22.

mm Hg ($P<0.001$) in mean arterial pressure during the infusion of alcohol and with the absence of a pressor effect during the second hour (Fig. 1 and 2 and Table 1).

In contrast to its effects on alcohol-induced sympathetic activation, dexamethasone did not alter sympathetic responses to the Valsalva maneuver or to immersion of the hand in ice water. The peak sympathetic responses during a Valsalva maneuver were 69±11 bursts per minute after placebo and 62±7 after dexamethasone. During immersion of the hand in ice water, the peak sympathetic responses were 37±7 and 43±4 bursts per minute, respectively.

Cardiovascular Responses to the Alcohol Infusion during Alpha-Adrenergic Blockade

During the infusions of alcohol and phentolamine, the blood-pressure response (Fig. 3) and vascular-resistance response in the calf (decreasing from 54±24 units at base line to 41±26 units at 120 minutes, $P=0.001$) mimicked those observed during the alcohol infusion after dexamethasone. In contrast, the peak response of the heart rate was more pronounced after phentolamine than after dexamethasone (88±20 vs. 69±7 beats per minute, $P=0.04$).

Cardiovascular and Sympathetic Responses to a Bolus Dose of Dexamethasone

Dexamethasone had no detectable effect on arterial pressure, heart rate, vascular resistance in the calf, or sympathetic-nerve discharge. The mean values at base line and two hours after dexamethasone administration were as follows: mean arterial pressure, 94±8 and 96±9 mm Hg; heart rate, 61±8 and 63±9 beats per minute; vascular resistance in the calf, 57±16 and 59±14 units; and sympathetic-burst frequency, 20±6 and 21±6 bursts per minute.

Discussion

We found that an infusion of alcohol roughly doubled the rate of sympathetic-nerve discharge and increased arterial pressure, and that these sympathoexcitatory and pressor effects were blocked by the administration of dexamethasone. These findings indicate that alcohol exerts a pressor effect in humans by causing sympathetic activation, an effect that is probably centrally mediated. The results of previous studies of the effects of alcohol on sympathetic activity were

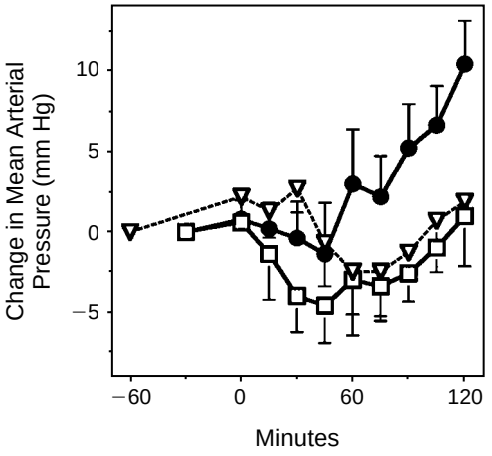

Figure 3. Mean (±SE) Changes in Arterial Pressure in Five Normal Subjects in Response to an Alcohol Infusion during the Administration of Placebo (●), Dexamethasone (□), or Phentolamine (▽).

Alpha-adrenergic blockade and the suppression of alcohol-induced sympathetic activation by dexamethasone had similar effects on the blood-pressure responses evoked by an infusion of alcohol ($P<0.001$ for the comparison of placebo with either dexamethasone or phentolamine).

conflicting.[5,7,8] Moreover, in the studies in which alcohol was administered orally, the relative sympathoexcitatory contributions of alcohol itself, alcohol-induced gastric irritation and distention, and stimulation of insulin release could not be distinguished.[23] Intravenous infusion of alcohol combined with direct measurement of sympathetic-nerve discharge allowed us to eliminate these confounding issues. Our results indicate that alcohol increases postganglionic sympathetic-nerve discharge and are consistent with the preliminary findings made after the oral administration of alcohol.[9]

Our results provide some mechanistic insight into alcohol-induced sympathetic activation. In rats, alcohol stimulates CRH release[13,14]; both alcohol[12] and CRH[18] exert sympathoexcitatory and pressor effects when administered centrally; and dexamethasone, presumably by inhibiting CRH release, attenuates stress-induced sympathetic activation.[18] In this study of humans, dexamethasone impaired the ability of alcohol to stimulate the discharge of sympathetic nerves. This response was not related to a nonspecific impairment of sympathetic responsiveness, since dexamethasone had no effect on either the base-line rate of sympathetic-nerve firing or responses to stimuli other than alcohol. Taken together, the results in animals and humans are consistent with the concept that sympathetic activation is related to a central neural action of alcohol, possibly involving CRH release.

The suppression of sympathetic activation markedly altered the cardiovascular responses to an infusion of alcohol. After the administration of placebo, alcohol increased sympathetic-nerve activity, did not affect vascular resistance in a limb, and increased the heart rate and mean arterial pressure. After the administration of dexamethasone, sympathetic activity did not increase, and alcohol caused vasodilation in the calf and a decrease in mean arterial pressure. These results are strengthened by the studies with phentolamine, which demonstrated the importance of sympathetic activation in mediating alcohol-induced pressor responses, and they have implications for the effects of alcohol on blood pressure in patients who either have autonomic dysfunction or are taking alpha-adrenergic–blocker drugs.

Increases in the heart rate during the administration of alcohol are thought to be mediated sympathetically because they are abolished by propranolol.[24] In our study, increases in the heart rate after dexamethasone were similar to those after placebo, not greater, even though suppression of the pressor response would be expected to result in the removal of baroreflex restraint on heart-rate responses (as evidenced by the greater response in the heart rate during the infusion of alcohol in the phentolamine studies). Therefore, it appears that dexamethasone also attenuated alcohol-induced stimulation of sympathetic outflow to the heart.

Alcohol consumption is associated with an increased incidence of hypertension[4-6] and stroke.[1-3] Although many factors have been implicated in the pathogenesis of alcohol-induced cardiovascular complications,[1,25] sympathetic activation could conceivably trigger acute events by promoting short-term increases in blood pressure and platelet aggregation.[26,27] Whether sympathetic activation also contributes to long-term elevation of arterial pressure in persons who drink alcohol every day needs further investigation, but results from studies of rats suggest that this could be the case.[11]

We are indebted to Drs. Laurent Vollenweider and Reza Owlya for assistance with some of these studies.

References

1. Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. N Engl J Med 1986;315:1041-6.
2. Hillbom M, Kaste M. Ethanol intoxication: a risk factor for ischemic brain infarction. Stroke 1983;14:694-9.
3. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: the Honolulu heart program. JAMA 1986;255:2311-4.
4. Klatsky AL, Friedman GD, Siegelaub AB, Gérard MJ. Alcohol consumption and blood pressure: Kaiser–Permanente Multiphasic Health examination data. N Engl J Med 1977;296:1194-200.
5. MacMahon S. Alcohol consumption and hypertension. Hypertension 1987; 9:111-21.
6. Klag MJ, He J, Whelton PK, Chen J-Y, Quian M-C, He G-Q. Alcohol use and blood pressure in an unacculturated society. Hypertension 1993;22:365-70.
7. Arkwright PD, Beilin LJ, Vandongen R, Rouse IA, Lalor C. The pressor effect of moderate alcohol consumption in man: a search for mechanisms. Circulation 1982;66:515-9.
8. Howes LG, Reid JL. The effects of alcohol on local, neural and humoral cardiovascular regulation. Clin Sci 1986;71:9-15.
9. Grassi GM, Somers VK, Renk WS, Abboud FM, Mark AL. Effects of alcohol intake on blood pressure and sympathetic nerve activity in normotensive humans: a preliminary report. J Hypertens Suppl 1989;7:S20-S21.
10. Zhang X, Abdel-Rahman ARA, Wooles WR. A differential action for ethanol on baroreceptor reflex control of heart rate and sympathetic efferent discharge in rats. Proc Soc Exp Biol Med 1988;187:14-21.
11. Russ R, Abdel-Rahman A-RA, Wooles WR. Role of the sympathetic nervous system in ethanol-induced hypertension in rats. Alcohol 1991;8:301-7.
12. Zhang X, Abdel-Rahman AA, Wooles WR. Impairment of baroreceptor reflex control of heart rate but not sympathetic efferent discharge by central neuroadministration of ethanol. Hypertension 1989;14:282-92.
13. Rivier C, Bruhn T, Vale W. Effect of ethanol on the hypothalamic-pituitary-adrenal axis in the rat: role of corticotropin-releasing factor (CRF). J Pharmacol Exp Ther 1984;229:127-31.
14. Rivier C, Imaki T, Vale W. Prolonged exposure to alcohol: effect on CRF mRNA levels, and CRF- and stress-induced ACTH secretion in the rat. Brain Res 1990;520:1-5.
15. Jenkins JS, Connolly J. Adrenocortical response to ethanol in man. BMJ 1968;2:804-5.
16. Overton JM, Fisher LA. Central nervous system actions of corticotropin-releasing factor on cardiovascular function in the absence of locomotor activity. Regul Pept 1989;25:315-24.
17. Kurosawa M, Sato A, Swenson RS, Takahashi Y. Sympatho-adrenal medullary functions in response to intracerebroventricularly injected corticotropin-releasing factor in anesthetized rats. Brain Res 1986;367:250-7.
18. Brown MR, Fisher AL. Corticotropin-releasing factor: effects on the autonomic nervous system and visceral systems. Fed Proc 1985;44:243-8.
19. Scherrer U, Vollenweider P, Randin D, Jéquier E, Nicod P, Tappy L. Suppression of insulin-induced sympathetic activation and vasodilation by dexamethasone in humans. Circulation 1993;88:388-94.
20. Vollenweider P, Tappy L, Randin D, et al. Differential effects of hyperinsulinemia and carbohydrate metabolism on sympathetic nerve activity and muscle blood flow in humans. J Clin Invest 1993;92:147-54.
21. Vallbo AB, Hagbarth KE, Torebjörk HE, Wallin BG. Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. Physiol Rev 1979;59:919-57.
22. Scherrer U, Vissing SF, Morgan BJ, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med 1990; 323:693-9.
23. Berne C, Fagius J, Niklasson F. Sympathetic response to oral carbohydrate administration: evidence from microelectrode nerve recordings. J Clin Invest 1989;84:1403-9.
24. Nakano J, Prancan AV. Effects of adrenergic blockade on cardiovascular responses to ethanol and acetaldehyde. Arch Int Pharmacodyn Ther 1972;196: 259-68.
25. Altura BM, Altura BT, Gebrewold A. Alcohol-induced spasms of cerebral blood vessels: relation to cerebrovascular accidents and sudden death. Science 1983;220:331-3.
26. Clayton S, Cross MJ. The aggregation of blood platelets by catecholamines and by thrombin. J Physiol (Lond) 1963;169:82P-83P.
27. Sloan JA, Hooper M, Izzo JL Jr. Effects of circulating norepinephrine on platelets, leukocyte and red blood cell counts by alpha1-adrenergic stimulation. Am J Cardiol 1989;63:1140-2.