Physiol. Psychol. **4**, 395 (1976); J. A. Harvey and I. Gormezano, *Soc. Neurosci. Abstr.* **7**, 359 (1981).
11. P. R. Solomon and K. E. Gottfried, *J. Comp. Physiol. Psychol.* **95**, 322 (1981).
12. S. D. Berry and R. F. Thompson, *Science* **205**, 209 (1979).
13. R. L. Isaacson, in *Inhibition and Learning*, R. A. Boakes and M. S. Halliday, Eds. (Academic Press, New York, 1972); P. R. Solomon, *Physiol. Psychol.* **8**, 254 (1980).
14. C. Stumpf, H. Petsche, C. Gogolak, *Electromyogr. Clin. Neurophysiol.* **14**, 212 (1962).
15. This dose disrupts both conditioning and hippocampal theta (*10, 14*).
16. For details of threshold tests see Solomon and Gottfried (*11*).
17. For a summary of histological and reconstruction procedures see Solomon (*8*).
18. See R. L. Isaacson [*The Limbic System* (Plenum, New York, 1974)] for a general discussion of this issue.
19. D. G. Lavond, D. A. McCormick, G. A. Clark, D. T. Holmes, R. F. Thompson, *Physiol. Psychol.* **9**, 335 (1981); J. W. Moore and J. E. Desmond, *Physiol. Behav.* **28**, 1029 (1982).
20. D. A. McCormick, D. G. Lavond, G. A. Clark, R. E. Kettner, C. E. Rising, R. F. Thompson, *Bull. Psychon. Soc.* **18**, 103 (1981).
21. Supported by NIMH grant MH33381 and NSF fellowship SPI-79 14900. We thank D. A. Haley and R. Ellis for their help with the study.

4 June 1982; revised 27 October 1982

Alcohol-Induced Spasms of Cerebral Blood Vessels: Relation to Cerebrovascular Accidents and Sudden Death

Abstract. *Ethyl alcohol produced graded contractile responses in rat cerebral arterioles and venules in vivo and in isolated canine basilar and middle cerebral arteries at a concentration range (10 to 500 milligrams per deciliter) which parallels that needed for its graded effects of euphoria, mental haziness, muscular incoordination, stupor, and coma in humans. Two specific calcium antagonists, nimodipine and verapamil, prevented or reversed the alcohol-induced cerebrovasospasm and thus may prove valuable in treating the hypertension and stroke observed in heavy users of alcohol.*

Ethyl alcohol contributes to numerous deaths and is a leading cause of fatal vehicular accidents, particularly among the young (*1*). Ongoing clinical studies in the United States and Scandinavia indicate a higher than normal incidence of hemorrhagic stroke and aneurysmal subarachnoid hemorrhage among heavy users of alcohol; such episodes may occur within 24 hours of a drinking binge (*2–5*). Several investigators have suggested that excessive alcohol consumption predisposes humans to stroke and sudden death (*2–4, 6, 7*).

Epidemiological and clinical evidence indicates that alcoholics in the later stages have a high incidence of hypertensive vascular disease (*7, 8*). However, it is difficult to associate the development of hypertension with the incidence of stroke and aneurysmal subarachnoid hemorrhage in "binge drinkers" (*2–6*). Moreover, it is not known why hypertension develops in alcoholics.

Chronic abuse of alcohol also produces atrophy of cortical, subcortical, and cerebral areas in the brain, brain damage, blackouts, functional neuronal deficits, psychoses, and hallucinations (*9, 10*). These changes in alcoholics, like the hypertension, have not been adequately explained.

Since cerebral hypoxia may play a role in the psychotomimetic actions of hallucinogens (*11*) and since alcoholics exhibit alterations in regional cerebral blood flow (*12*), we wondered whether alcohol can exert direct actions on cerebral blood vessels. We report that alcohol can produce vasospasm in intact cerebral arterioles and venules and in isolated cerebral arteries at concentrations that induce intoxicating, psychotomimetic, or lethal effects in humans. The contractile effects of alcohol on cerebral blood vessels can be abrogated by use of calcium antagonists (nimodipine or verapamil).

For the in vivo studies, the diameters of pial arterioles and venules in male Wistar rats (*13*) were measured quantitatively with an image-splitting television microscope recording system (*14*). Responsiveness of selected arterioles (17 to 58 μm) and venules (22 to 55 μm) was tested before and after administration of alcohol topically, intra-arterially, intraperitoneally, or intravenously.

For the in vitro studies, helical strips 10 to 15 mm long by 1.5 to 2.0 mm wide were cut from segments of canine middle cerebral and basilar arteries, suspended isometrically under 1 g of tension, and incubated in chambers containing normal Krebs-Ringer bicarbonate solution (37°C) through which a mixture of 95 percent O_2 and 5 percent CO_2 was bubbled (*15*). Graded concentrations of alcohol were then added to the bathing solution. Contractional force was measured with Grass FT-03 force-displacement transducers and recorded on a Grass model 7 polygraph.

Perivascular, intracarotid, or systemic administration of graded doses of ethanol resulted in rapid and graded constriction of all cortical arterioles examined (Fig. 1 and Table 1). Local administration of alcohol at concentrations between 10 and 50 mg/dl produced threshold constriction of the arterioles. Such effects, and those produced by concentrations of alcohol up to approximately 200 mg/dl, gradually disappeared within 5 to 40 minutes, depending on the dose. Doses of alcohol that resulted in perivascular or blood concentrations greater than 300 mg/dl usually resulted in arteriolar spasms that were irreversible and often followed by rupture within 5 to 10 minutes, leading to focal hemorrhages. Perivascular or intracarotid administration of 0.01 to 1 percent ethanol produced a concentration-related vasoconstriction of cortical venules, with an 8 to 60 percent reduction in vessel diameter ($N = 8$ animals); doses of ethanol above 0.3 percent often resulted in irreversible spasm and rupture. Blood flow in cortical microvessels was curtailed markedly.

Table 1. Alcohol-induced vasoconstriction of rat cortical arterioles in vivo. Alcohol was administered to the surface of the brain in 0.1-ml volumes or intraperitoneally in doses of 0.5, 1.0, 2.0, or 4.0 g/kg. Observations were made 30 to 60 minutes after systemic (intraperitoneal) administration of alcohol. All experimental values are significantly different from the corresponding control values ($P < .001$, paired t-test). Values are means ± standard errors for eight rats per group.

Route of administration and dose	Arteriolar diameter (μm)		Reduction (%)
	Before alcohol	After alcohol	
Perivascular			
Cerebrospinal fluid (0.1 ml)	27.4 ± 0.57	27.5 ± 0.56	0
10 mg/dl	27.5 ± 0.56	24.0 ± 0.50	12.7
25 mg/dl	27.4 ± 0.52	22.5 ± 0.42	17.8
100 mg/dl	27.3 ± 0.53	21.7 ± 0.38	20.5
250 mg/dl	27.3 ± 0.53	20.8 ± 0.35	23.8
1000 mg/dl	27.5 ± 0.56	20.2 ± 0.34	26.5
Systemic			
Saline	38.2 ± 0.72	38.4 ± 0.73	0
0.5 g/kg	38.0 ± 0.72	34.2 ± 0.66	10
1.0 g/kg	38.4 ± 0.74	30.4 ± 0.58	20.8
2.0 g/kg	38.2 ± 0.72	26.2 ± 0.46	31.4
4.0 g/kg	38.0 ± 0.71	24.6 ± 0.42	35.2

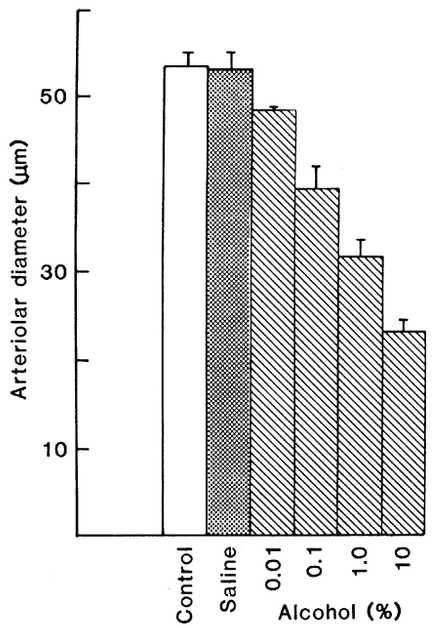

Fig. 1. Alcohol-induced vasoconstriction of rat cortical arterioles in vivo. Different doses of alcohol were infused through the carotid artery at a constant rate of 0.02 ml/min. Observations were recorded for 30 to 45 seconds every 2 minutes over a period of 30 minutes beginning with each infusion. Vessel diameters were affected by alcohol within seconds. All experimental values are significant at $P < .001$. Values are means ± standard errors for six rats per group. Similar results were obtained irrespective of whether sodium pentobarbital or ketamine hydrochloride was used as the anesthetic.

Intramuscular injection of pharmacological antagonists that act on serotoninergic receptors (methysergide, 1.0 mg/kg), cholinergic receptors (atropine, 2.0 mg/kg), histaminergic receptors (diphenhydramine HCl or metiamide, 1.0 mg/kg), or alpha-adrenergic receptors (phentolamine, 1.0 mg/kg) 30 minutes before testing did not inhibit the ethanol-induced vasospasms ($N = 5$) (*16*); nor did intravenous injection of a cyclo-oxygenase inhibitor, indomethacin (1 mg/kg) ($N = 5$).

Addition of alcohol to the physiological salt solution bathing the isolated canine cerebral arteries resulted in a rapid increase in tension in all arteries tested, an increase similar to that induced by potassium ions (Fig. 2). A concentration of ethanol as low as 8 m*M* (approximately 37 mg/dl) usually produced contractions in the arteries. Thus the threshold concentrations for cerebral arterioles in vivo and isolated cerebral arteries were similar. In humans, blood alcohol concentrations of 35 to 40 mg/dl appear after the ingestion of less than 1 ounce of whiskey, producing some degree of euphoria, light-headedness, mental haziness, and talkativeness, with little impairment in memory or arithmetic problem-solving (*17*). The concentrations of alcohol that caused moderate to strong spasms of cerebral arterioles and venules (85 to 210 mg/dl) are associated with slurring of speech, nystagmus, muscular incoordination, tremor, impairment of vision, and unsteadiness of gait (*17*). The higher vasoactive levels of alcohol (> 250 mg/dl), which produced intense spasm, and often rupture, of cortical arterioles and venules, are identical to those concentrations found in the blood of humans with alcohol-induced stupor, coma, and stroke-like episodes (*2–5, 7, 17*).

Our observations in vivo and in vitro support the suggestion (*18*) that ethanol produces hypoxia in the brain by affecting the cerebral circulation. They also may explain the higher than normal incidence of hypertension in chronic alcoholics and the higher than normal incidence of cerebrovascular accidents and sudden death in binge drinkers. So far, it has been difficult to account for the elevation in blood pressure observed in chronic alcoholics on the basis of age, sex, obesity, smoking, plasma high-density lipoprotein, catecholamines, or heredity (*4, 7, 8*). Likewise, none of these factors can account for the incidence of stroke in binge drinkers, particularly among the young (*2–6*). Because curtailment of blood flow to the central nervous system may result in hypertension (*19*) and because prolonged cerebral vasospasm can lead to brain ischemia and rupture of cerebral vessels, our findings may cast light on the etiology of alcohol-induced hypertension and stroke, particularly since both are often associated with one another (*2–8*).

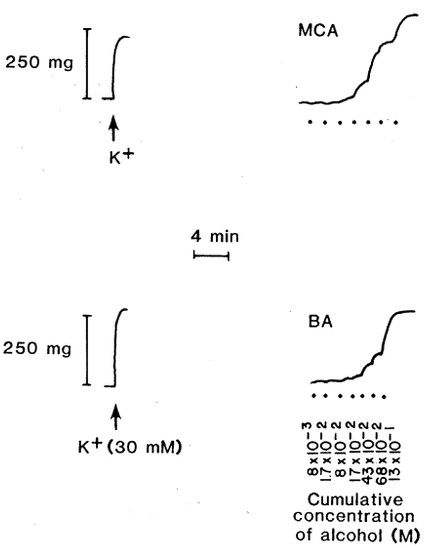

Fig. 2. Typical responses of a canine middle cerebral artery (*MCA*) and a basilar artery (*BA*) to addition of KCl and alcohol.

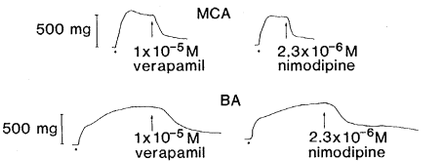

Fig. 3. Rapid relaxation of alcohol-induced cerebral arterial spasms by verapamil and nimodipine. Recording speed is the same as in Fig. 2. Alcohol (170 m*M*) was added at dot in all cases.

All contractile events in muscle tissue are mediated by an elevation in the cytoplasmic level of calcium ions. Addition of the calcium antagonist nimodipine or the calcium antagonist verapamil (10^{-8} to $10^{-5}M$) completely reversed or prevented spasms in all eight cerebral arteries tested (Fig. 3). If these findings hold true for human cerebral blood vessels, then calcium antagonists may be of value in the treatment of alcohol-induced cerebrovascular disorders.

BURTON M. ALTURA
BELLA T. ALTURA
ASEFA GEBREWOLD

Department of Physiology,
State University of New York,
Downstate Medical Center,
Brooklyn 11203

References and Notes

1. R. K. Jones and K. B. Joscelyn, *Alcohol and Highway Safety, 1978: A Review of the State of Knowledge* (Report UM-HSRI-78-5, University of Michigan Highway Safety Institute, Ann Arbor, 1978); D. W. Clark and B. MacMahon, *Preventive and Community Medicine* (Little, Brown, Boston, 1982).
2. M. Hillbom and M. Kaste, *Lancet* **1978-II**, 1181 (1978).
3. K. Lee, *Acta Neurol. Scand.* **59**, 270 (1979).
4. M. J. Ashley and J. G. Rankin, *J. Stud. Alcohol* **41**, 1040 (1980).
5. M. Hillbom and M. Kaste, *Stroke* **12**, 422 (1981).
6. H. Pakkenberg, *Acta Psychiatr. Neurol. Scand.* **29**, 237 (1954); J. R. Taylor, *N. Engl. J. Med.* **306**, 1111 (1982).
7. J. D. Mathews, *Austr. N.Z. J. Med.* **9**, 201 (1979).
8. A. L. Klatsky, G. D. Friedman, A. B. Siegelaub, M. J. Gerard, *N. Engl. J. Med.* **296**, 1194 (1977); C. A. D'Alonzo and S. Pell, *J. Occup. Med.* **10**, 344 (1968); D. G. Beevers, *Lancet* **1977-II**, 114 (1977); E. Harburg, F. Ozoren, V. M. Hawthorne, A. Schork, *Am. J. Public Health* **70**, 813 (1980); P. N. Barboriak, A. J. Anderson, R. G. Hoffmann, J. J. Barboriak, *Alcoholism: Clin. Exp. Res.* **6**, 234 (1982).
9. J. N. Riley and D. W. Walker, *Science* **201**, 646 (1978); D. W. Walker, D. E. Barnes, S. F. Zornetzer, B. E. Hunter, P. Kubanis, *ibid.* **209**, 711 (1980); L. A. Cala and F. L. Mastaglia, *Alcoholism: Clin. Exp. Res.* **5**, 283 (1981).
10. M. A. Ron, *Br. Med. Bull.* **38**, 91 (1982); A. D. Thompson, *ibid.*, p. 87.
11. P. G. Bourne, *Acute Drug Abuse Emergencies* (Academic Press, New York, 1976); R. C. Meibach, S. D. Glick, R. Cox, S. Maayani, *Nature (London)* **282**, 625 (1979); B. T. Altura and B. M. Altura, *Science* **212**, 1051 (1981).
12. S. Shimojyo, P. Scheinberd, O. Reinmuth, *J. Clin. Invest.* **46**, 849 (1967); M. Berglund and J. Risberg, *Arch. Gen. Psychiatry* **38**, 351 (1981).
13. The rats were lightly anesthetized with sodium pentobarbital (25 mg/kg) or ketamine hydrochloride (80 mg/kg). Tracheostomies were per-

formed and catheters were placed in the femoral and internal carotid arteries for drug infusions and for the determination of blood gases (CO_2 and O_2 pressures) and blood pressure. A left or right craniotomy was then made and the dura was stripped away. Artificial cerebrospinal fluid (155 m*M* Na^+, 137 m*M* Cl^-, 21 m*M* HCO_3^-, 3.5 m*M* K^+, 1.3 m*M* Mg^{2+}, 2.2 m*M* Ca^{2+}, and 6.0 m*M* glucose) maintained at 36° to 37.5°C and *p*H 7.3 to 7.4, was allowed to drip onto the exposed brain surface. The temperature of the brain surface was kept close to 37.5°C, as measured with a thermistor probe. One-tenth of a milliliter of 5 percent $BaCl_2$ was administered as a test for normal vascular reactivity (*14*).

14. B. M. Altura, A. Gebrewold, S. Lassoff, *Br. J. Pharmacol.* **69**, 543 (1980); B. M. Altura, *J. Pharmacol. Exp. Ther.* **193**, 403 (1975).
15. B. T. Altura and B. M. Altura, *Neurosci. Lett.* **20**, 323 (1980).
16. B. M. Altura and A. Gebrewold, *Br. J. Pharmacol.* **73**, 580 (1981); B. M. Altura, *Microvasc. Res.* **3**, 361 (1971).
17. H. Kalant, in *International Encyclopedia of Pharmacology and Therapeutics*, J. Trémolières, Ed. (Pergamon, New York, 1970) vol. 1, section 20, p. 189.
18. H. Goldman, L. A. Sapirstein, S. Murphy, J. Moore, *Proc. Soc. Exp. Biol. Med.* **144**, 983 (1973).
19. B. Folkow, *Physiol. Rev.* **62**, 347 (1982).

20. This work was supported in part by PHS research grants DA02339 and HL29600 from the Public Health Service.

10 November 1982; revised 24 January 1983

Drug History Modifies the Behavioral Effects of Pentobarbital

Abstract. *Behavior of squirrel monkeys, maintained by the termination of stimuli associated with electric shock, was suppressed by response-dependent shock delivery. The effects of pentobarbital on this behavior depended on whether monkeys had previously received morphine. In monkeys without experience with drugs, pentobarbital increased responding. In monkeys with recent experience with morphine, however, pentobarbital resulted in a smaller increase or decrease in responding. The rate-decreasing effects of pentobarbital after a history of morphine administration could be reversed by the administration of* d*-amphetamine. These findings suggest that the behavioral effects of abused drugs may depend on previous experience with other drugs, even when those drugs are from a different pharmacological class.*

Although the behavioral effects of many drugs are frequently influenced by the relationship between behavior and its immediate consequences (*1*), several studies have recently found that prior experience can markedly change the effect of a drug on behavior. For example, the usual effects of *d*-amphetamine on behavior suppressed by electric shock can be completely reversed after exposure to a condition in which responding postpones shock (*2*). These and other findings (*3*) have suggested that the behavioral effects of drugs may, under some conditions, depend more on past experience than on either the current environment or the prevailing behavior. We now report that prior experience with one psychoactive drug can determine the behavioral effects of a different drug. Thus, drug history, like behavioral history, can dramatically alter the effects of drugs.

Drug effects were studied in four male squirrel monkeys (*Saimiri sciureus*). All monkeys were experimentally naïve and weighed between 0.8 and 1.0 kg. During 2-hour experimental sessions, the monkeys were seated in a standard Plexiglas restraining chair, which lightly restrained the animal at the waist. The chair was equipped with 7-W white stimulus lamps, a response lever (BRS/LVE 1352), a feedback relay, and brass shock electrodes. Shock (7 mA, 200 msec, 650 V, and 60 Hz) was delivered through series resistance to the tail.

Shocks were initially delivered every 5 seconds; responding postponed shock for 25 seconds (*4*). After responding had been established (approximately 14 sessions), the shock-postponement procedure was replaced with a fixed-interval schedule under which responding terminated the stimulus lights correlated with shock (stimulus-shock termination) (*5*). Under the termination schedule, shocks were arranged to occur every 3 seconds, beginning 3 seconds after the 5-minute interval elapsed. The first response after the 5-minute interval terminated the shock-correlated stimuli and produced a 60-second period during which responding had no scheduled consequences and shocks never occurred. After responding stabilized, an additional consequence was added to the termination schedule: each thirtieth response

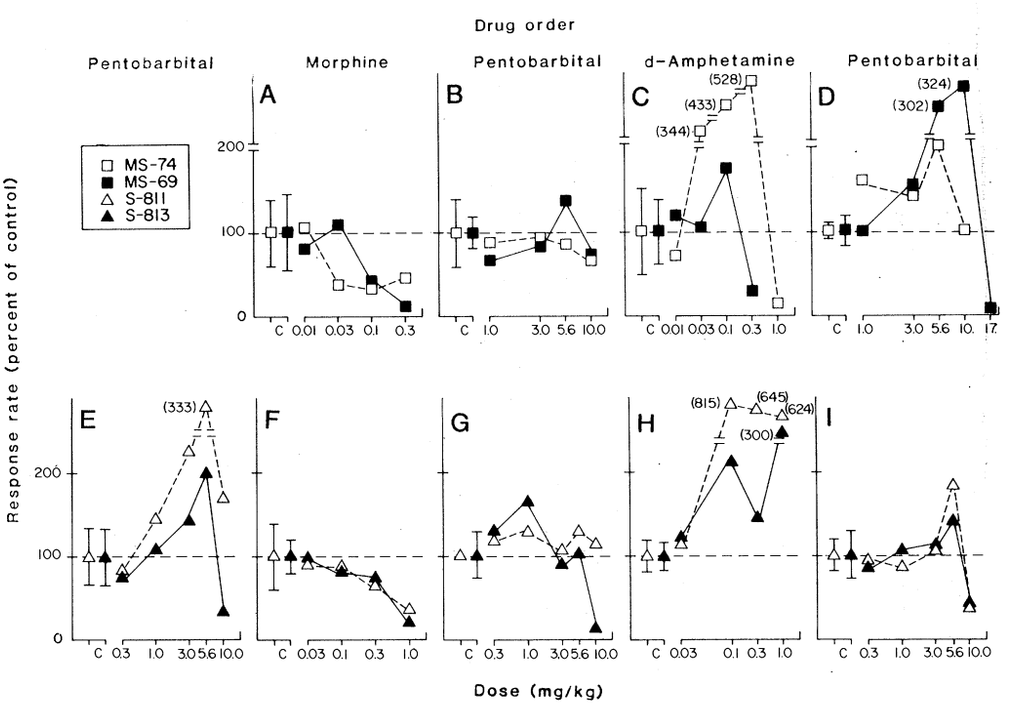

Fig. 1. Dose-effect functions for responding simultaneously (i) maintained under a fixed-interval 5-minute stimulus-shock termination schedule and (ii) suppressed by a fixed-ratio 30-response shock-presentation schedule. Drug effects are expressed as a percentage of control rates (Table 1). Each point represents the mean of two determinations for each subject. Vertical bars represent 1 standard deviation from the mean of all control rates of responding (Thursdays) during the determination of the effects of that drug.