certain anatomical evidence which, although scanty, does indicate that vagal fibers do reach the ventricles (*5*), (ii) the report that the ventricular rate may diminish during vagal stimulation in dogs with complete atrioventricular block (*6*), (iii) the well-known depressing action of acetylcholine upon ventricular contractility (*2*, *6*), and (iv) the observation that acetylcholine is synthesized in the ventricles as well as in the atria (*7*).

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Monoamine Oxidase Inhibitors: Augmentation of Pressor Effects of Peroral Tyramine

Abstract. *Monoamine oxidase inhibitors markedly enhance the oral pressor potency of tyramine by preventing it from being destroyed by the monoamine oxidase normally present in liver and intestine. Since certain types of cheese contain high concentrations of tyramine, they should not be eaten by patients during treatment with a monoamine oxidase inhibitor.*

A fairly common side effect associated with therapy with monoamine oxidase inhibitors is orthostatic hypotension (*1*, *2*). Recently, a number of investigators have reported the occurrence of paradoxical hypertension after administering a monoamine oxidase inhibitor. This report is concerned with a mechanism that may be in part responsible for this effect.

Adult male albino rats (Wistar strain) weighing 200 to 400 g were treated orally with various doses of tranylcypromine once a day for 2 days, or pargyline or iproniazid, once a day for 3 days. After treatment the rats were anesthetized intravenously with pentobarbital (45 mg/kg) and arterial blood pressure was recorded from the carotid artery. The arterial pressure was permitted to stabilize over a 15-minute interval after which the rats were treated with various doses of tyramine by gastric intubation. Blood pressure was recorded continuously until either a maximum change in pressure had been achieved or until a 20-minute period had elapsed after treatment with tyramine. Mean changes in systolic, mean, and diastolic pressure were determined for each dose of each drug. A control group of rats was tested in the same manner as the treated rats. The results of these experiments are summarized in Table 1.

In control rats it was found necessary to increase the dose of tyramine above 25 mg per kilogram of body weight in order to evoke a pressor response significantly greater than that caused by gastric intubation with an equivalent volume of saline. In general, the increase in blood pressure which occurred after tyramine administration came on approximately 5 to 10 minutes after its gastric intubation.

All of the monoamine oxidase inhibitors tested permitted a reduction in the dose of tyramine necessary to evoke a significant pressor response. Although the time for onset of the pressor response was similar to that for the controls, the duration of the response was generally more prolonged.

The data clearly demonstrate that monoamine oxidase inhibitors can markedly potentiate the pressor response to orally administered tyramine. Presumably this is accomplished by inhibition of liver or intestinal monoamine oxidase, or both. Thus inhibition of monoamine oxidase may permit doses of tyramine which would normally be destroyed in the liver or intestine to enter the systemic circulation and evoke a pressor response through the release of norepinephrine (*3*). In the absence of a monoamine oxidase inhibitor, 4 to 16 times as much tyramine is required to evoke a pressor response. It is assumed that such relatively high doses of tyramine eventually block monoamine oxidase activity by providing excessive substrate which, in turn, permits sufficient tyramine to penetrate the systemic circulation, thereby evoking a pressor response.

Table 1. Effect of monoamine oxidase inhibitors on the pressor response to orally administered tyramine. A minimum of six rats were tested for each dose of tyramine.

Dose of tyramine (mg/kg)	Mean pressor response (mm-Hg) ± S.E.		
	Systolic	Mean	Diastolic
	Normal (no inhibitor)		
0	8.6 ± 4.5	5.1 ± 4.5	5.0 ± 4.1
25.0	5.0 ± 2.6	1.8 ± 2.1	1.5 ± 2.2
50.0	34.7 ± 11.2	23.3 ± 7.0	17.8 ± 5.1
	Tranylcypromine 0.5 mg/kg per day (2 days)		
3.0	5.6 ± 2.6	5.4 ± 1.8	5.0 ± 1.6
6.0	10.7 ± 4.8	9.8 ± 4.2	8.3 ± 4.0
	Tranylcypromine 1.0 mg/kg per day (2 days)		
3.0	9.8 ± 3.2	7.7 ± 2.8	7.6 ± 2.8
6.0	*54.4 ± 10.1	*40.8 ± 6.8	*37.5 ± 5.6
12.5	*46.9 ± 13.4	*36.5 ± 9.7	*31.8 ± 8.5
25.0	*47.5 ± 5.9	*34.2 ± 4.5	*27.5 ± 4.2
	Tranylcypromine 2.0 mg/kg per day (2 days)		
3.0	*26.6 ± 8.0	*28.4 ± 16.4	*26.0 ± 14.3
6.0	*44.2 ± 12.4	*36.7 ± 11.9	*37.5 ± 11.4
	Iproniazid 50 mg/kg per day (3 days)		
3.0	20.0 ± 8.7	16.6 ± 8.0	15.0 ± 7.6
6.0	*30.0 ± 12.4	*22.2 ± 8.7	*19.2 ± 7.4
12.5	*36.0 ± 15.3	*29.0 ± 13.6	*28.0 ± 12.1
	Pargyline 100 mg/kg per day (3 days)		
6.0	8.7 ± 4.2	8.5 ± 3.7	7.5 ± 3.6
12.5	*59.2 ± 13.7	*52.5 ± 9.1	*45.8 ± 9.1

* Significant increase over control response to 25 mg/kg of tyramine.

Certain specific types of cheese contain relatively high concentrations of tyramine (*4*). Depending on the concentration of the tyramine in the cheese and the amount of cheese ingested, it is quite conceivable that a sufficient amount of tyramine could be ingested to precipitate a marked hypertensive response in a patient whose monoamine oxidase is blocked. Indeed, a number of clinical investigators (*5*) have already called attention to the fact that patients being treated with monoamine oxidase inhibitors have experienced hypertensive crises after ingestion of cheese known to contain large amounts of tyramine.

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Hypothermia, Asphyxia, and Cardiac Glycogen in Guinea Pigs

Abstract. *Cardiac glycogen was not affected by cooling guinea pigs for short periods. In normothermic animals it was reduced 75 percent or more at the time of death from asphyxia. Quickly cooled animals asphyxiated until the time of death of warm controls showed no significant losses of cardiac glycogen; animals cooled while breathing 10 percent oxygen plus 5 percent carbon dioxide showed slight reductions. Therefore, hypothermia spares cardiac glycogen during asphyxia, but there are factors other than cardiac glycogen which influence survival of asphyxiated animals.*

Hypothermia has been found to be the most effective treatment we have tested in preventing death from asphyxia in experimental animals (*1–4*). For example, puppies at 15°C body temperature live on the average 7½ times as long as normothermic littermates and many recover without assistance from 2½ hours in 95 percent N_2 plus 5 percent CO_2 (10 times the lethal exposure for warm littermates) (*3, 5*). Cooling also has been tried successfully on more than 130 asphyxiated human infants that had previously failed to respond to the usual resuscitative measures (*5, 6*). As indicated by the learning and memory of a conditioned avoidance response in rats, cooling, if adequate, not only saves lives but also protects brain function as well. Some impairment was found in the rats in which cooling was minimal, that is, lowest temperatures were above 32°C. None was found in those whose temperatures fell to 31°C or less (*7*).

Because of the precise relationship found by Stafford and Weatherall (*8*) between cardiac glycogen and the length of survival of rats in nitrogen, these workers suggested that the limiting factor in anoxic survival might be the initial carbohydrate concentration in the heart. Accordingly, it became important to ascertain whether or not the protection conferred by hypothermia against asphyxia was reflected by a similar protection against the depletion of cardiac glycogen caused by the asphyxia.

The experimental material consisted of unanesthetized young adult male guinea pigs (weighing 300 g) which had been fasted for 24 hours, and day-old neonates of the same species. The animals were asphyxiated in a bell jar through which was flowing a stream of 95 percent N_2 plus 5 percent CO_2 at a rate of 10 liters or more per minute. Both the warm and the cooled experimental animals were killed immediately after the time of last gasp of the warm animals. The adult animals were killed by a blow on the head and the neonates by decapitation with a guillotine. At the time they were killed the body temperature of the warm controls was 37°C and that of the cooled animals was between 23°C and 25°C. While one investigator rapidly dissected the gastrocnemii, another excised the liver, the heart, and the diaphragm. The liver and the heart were quick-frozen immediately after removal; the gastrocnemii and diaphragm were frozen simultaneously somewhat later. Rapid freezing was accomplished by compression between two blocks of CO_2 ice (minus 79°C) and the freezing time was recorded as seconds after decapitation. Since guinea pigs cooled under hypoxia-hypercapnia live approximately 50 percent longer than those cooled in air (*5, 9*), in the experiments with adults two additional groups of animals were cooled to 25°C in an atmosphere of 10 percent O_2 plus 5 percent CO_2 (while subjected to hypoxia-hypercapnia). The animals in one group were killed without further treatment in order to test the effects of the method of cooling on glycogen content. Those in the other group were asphyxiated for the same length of time as the normothermic experimental animals.

Litters of three were used for the experiments on newborn animals. One animal in each litter, which served as the control, was killed while normothermic. The second was asphyxiated while normothermic and decapitated immediately after its last gasp. The third was cooled to approximately 25°C and killed after asphyxiation for the same length of time as in the case of the second animal.

Glycogen was determined by the anthrone method of Morris (*10*) as modified by Russell and Bloom (*11*) and by use of Russell's "routine reagent A" (*12*).

The effects of cooling and of cooling combined with hypoxia-hypercapnia on cardiac glycogen of adult animals are summarized in Table 1. The table shows that rapid cooling by immersion in ice water was not associated with loss of glycogen from the heart. However, when the cooling was accompanied by exposure to 10 percent O_2 plus 5 percent CO_2 plus 85 percent N_2 (hypoxia-hypercapnia) there was a statistically significant fall in cardiac glycogen of 30 percent (from 6.3 $\pm$ 0.72 mg/g to 4.4 $\pm$ 0.27 mg/g). The normothermic animals which were asphyxiated until their last gasp (hearts frozen 70 seconds later) lost 75 percent of the glycogen from the ventricles (a reduction from 6.3 mg/g to 1.6 mg/g). The quickly cooled hypothermic animals asphyxiated for the same length of time showed no loss of cardiac glycogen when frozen 74 seconds after stunning. Under the same experimental conditions, the cardiac glycogen of the animals which were cooled with hypoxia and hypercapnia averaged less than that of the group which was cooled while breathing air, but the difference was not statistically significant (5.9 $\pm$ 0.43