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Comparison of Glycerol and Trehalose as Nutrients for the Growth of Tubercle Bacilli.*

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Glycerol is recognized as the most valuable organic nutrient for the growth of tubercle bacilli. The studies of Anderson,[1] however, show that the lipins which make up a large part of the structure formed by these bacilli in the course of growth are not glycerides, but in considerable measure are esters of trehalose. It therefore seemed of interest to see if trehalose might function more effectively than glycerol in promoting growth. Trehalose for the experiment was furnished by Dr. Anderson.

Two lots of Long's[2] synthetic medium were made up, one containing 5% of glycerol and the other 5% of trehalose instead of glycerol. Both lots were sterilized in the autoclave at 15 lb for 30 min. They were tested for reducing sugars after autoclaving and found negative. All flasks were inoculated with an equal amount of fresh tubercle bacillus culture (A-21), and incubated at 37.5°C for 58 days.

At the end of this time there was visibly less growth on the trehalose culture medium than on the glycerol medium. The total growth from each flask was filtered through tarred filter paper, air dried for several weeks, and weighed. The average dry weight of bacilli per 200 cc of the regular Long's medium containing glycerol was 1.580 g, and that from the same medium with trehalose substituted for glycerol was 0.985 g.

It thus does not appear that preformed trehalose has any advantages over glycerol as a constituent of the culture medium for tubercle bacilli.

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1 Anderson, R. J., *Chem. Rev.*, 1941, **29**, 225.

2 Long, E. R., and Seibert, F. B., *Am. Rev. Tubere.*, 1926, **13**, 393.

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Effects of Intravenous Injections of L-Dopa upon Blood Pressure.*

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It has been reported by Bing and Zucker[1] that a rise in blood pressure is produced by the injection of l-dopa into the renal artery or directly into the renal parenchyma of cats after the kidneys of these animals have been made hypoxic by temporarily arresting the arterial blood supply. The rise in blood pressure has been attributed to a disturbance in the amino acid metabolism in the kidney. Normally in this organ aromatic amino acids are first decarboxylated to form amines with pressor properties, and the latter are then deaminized. Under anærobic conditions, although the decarboxylation is not affected, the deaminization does not take place (Holtz *et al.*).[2] As a result in the chronic ischemic kidney the pressor amines enter the blood

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1 Bing, R. J., and Zucker, M. B., *Am. J. Phys.*, 1941, **133**, P214.

2 Holtz, P., Heise, C., and Luedtke, C., *Arch. Exp. Path. u. Pharm.*, 1938, **191**, 87.

stream and produce a rise in blood pressure. This absence of deaminization in chronic renal ischemia is also thought to be a factor in the production of animal experimental hypertension *per se*.

The work cited suggested that a similar mechanism might obtain in human essential hypertension, and a study of the mechanism in patients with this disease was, therefore, undertaken. Since injection directly into the renal artery in humans is highly impractical, it was first necessary to determine if peripheral intravenous injections‡ in hypertensive cats would produce the same effect as did the renal intra-arterial injections. The effect of l-dopa via intravenous injection was then studied in 4 normal cats, and again after acute renal ischemia was produced in the 4 cats by applying Goldblatt clamps to both renal arteries. Following this the right kidney was removed from each animal, the left renal artery clamp was left untouched. Three animals survived and developed hypertension. These animals were injected with l-dopa 10 days after operation, at which time their basal blood pressure readings averaged 40 mm above their original levels. The experiments were carried out while the animals were under nembutal anesthesia; the blood pressure was recorded by femoral artery cannulation.

Intravenous injection of 50 mg of l-dopa caused a marked rise, averaging 60 mm of mercury above the basal level, in the blood pressure of the hypertensive cats. The rise reached its maximum 4 min after the injection and persisted for a total of from 12 to 15 min. A second injection of l-dopa given after the maximum elevation had occurred caused no further increase in the blood pressure but prolonged the duration of the rise. The intravenous injection of 50 mg of l-dopa in the normal cats or cats with acute renal ischemia produced no rise in blood pressure. No untoward effects due to the dopa were observed in any of the cats.

Since these observations established the similarity in blood pressure response in hypertensive cats to peripheral intravenous and direct renal intra-arterial injections of l-dopa, a basis was given for a comparative study of the effect of intravenously administered l-dopa in human essential hypertension. Five patients with this malady and an equal number of patients with normal blood pressure were injected with the amino acid and the effect on the blood pressure was noted.

The hypertensive patients selected were individuals between the ages of 35 and 50 who had definite, but not excessive elevation of blood pressure. Hypertension was an incidental clinical finding in these patients. They presented no anamnestic or laboratory evidence of kidney damage, no signs or symptoms of cardiac decompensation, nor electrocardiographic changes indicative of myocardial damage. Each hypertensive patient was paired with a patient with normal blood pressure, both members of the pair receiving the same amount of l-dopa. The quantity injected varied between 100 and 450 mg dissolved in 10 to 30 cc of sterile physiological saline. In each experiment a quantity of saline equal to that used to dissolve the l-dopa was injected several minutes prior to the dopa injection to control the possible effect of the injection procedure itself on the blood pressure. The patients were kept in bed for at least several hours prior to, and also during the experiment. The blood pressure was measured at one minute intervals with the auscultatory method.

The injection of l-dopa in quantities of 120 mg or more produced a definite rise in the blood pressure of the hypertensive patients. The time of the onset after the injection, and the magnitude of the blood pressure rise bore a relationship to the amount of l-dopa injected. As may be seen in Table I, the larger the dose of the amino acid, the sooner the elevation in blood pressure occurred and the greater the magnitude of the elevation. No definite relationship could be ascertained between the amount of l-dopa used and the duration of the blood pressure increase.

The normotensive patient injected with 120 mg of l-dopa showed no elevation of blood pressure, although this amount of the

‡ A pressor response to intravenous injections of dopa in rats has been reported by Schroeder.[3]

[3] Schroeder, H. A., *J. Exp. Med.*, 1942, **75**, 523.

TABLE I.
Effect of Dopa Injection on Human Blood Pressure.

Pat.	Age	Basal B.P., mm Hg	Amt dopa inj., mg	Max. ht systolic pressure, mm Hg	Interval inj. to max. rise, min	Duration of rise, min	Max. rise of diastolic pressure, mm Hg	Side effect	Onset of side effect after inj., min
M.N.	49	134/74	80	0	—	0	0	0	—
V.A.	35	150/100	95	0	—	0	0	0	—
M.G.	45	110/66	120	0	—	0	0	0	—
S.M.	50	150/90	120	22	5.5	6	10	nausea, retching	4
E.S.	30	140/86	200	8	4.5	2	2	mild tachycardia	4
A.U.	42	174/90	200	30	4	6	6	mild tachycardia, tinnitus	2
G.S.	40	120/60	200	10	4	2.5	3	sweating, retching	4
R.T.	36	196/108	200	32	3	16	10	nausea	6
								vomiting	8
S.G.	39	112/70	450	18	2	13	8	sl. nausea	2
								vomiting	15
R.B.	41	170/105	450	35	1.5	15	15	nausea	4
								vomiting	7

amino acid had caused a rise in the hypertensive patient which lasted for 6 min and reached a maximum of 22 mm. Two normal patients injected with 200 mg of l-dopa exhibited rises of 8 and 10 as compared to 30 and 32 mm respectively in hypertensive patients who also received 200 mg of l-dopa. The duration of the rise in the normals was 2 and 2.5 min respectively, while that in the hypertensives was 6 and 16 min. The rise occurred slightly sooner in the hypertensives than in the normals. The injection of 450 mg in a normotensive patient produced a rise which lasted for 13 min and reached a maximum of 18 mm. In the hypertensive patient receiving the same dose there occurred a rise with a maximum of 35 mm and lasting 15 min. It will be noted that the injection in a hypertensive patient of 120 mg of dopa caused a higher rise than did the larger amounts including the 450 mg dose, in the patient with normal blood pressure.

Injection of 100 mg or less of l-dopa had no effect of the blood pressure of 2 patients with normal tension, and one patient with moderate hypertension. Two additional patients with marked hypertension, (B.P. 236/112 and 260/160), also showed no pressor response to small doses (75 and 100 mg) of l-dopa.

In addition to the pressor response side effects were observed in the patients injected with 120 mg or more of l-dopa. The hypertensive patient who received 120 mg experienced nausea and retching; the normotensive injected with this dose exhibited no side effects. One of the 2 patients with normal tension injected with 200 mg dopa had mild tachycardia, the other sweating and retching. Of the hypertensives receiving the same dose, one had mild tachycardia and tinnitus, the other nausea, vomiting and retching. Following the injection of 450 mg of dopa, both the normotensive and the hypertensive patient had nausea and vomiting. The vomiting caused no drop in blood pressure. In the majority of the cases, the side effects appeared after the maximum rise in blood pressure had developed. No other relationship of these side effects to the pressor effect could be established.

Discussion. Although the humans with essential hypertension received proportionally much smaller amounts of l-dopa than did the hypertensive cats, similar blood pressure responses were obtained in both. The similarity consisted in a rather abrupt definite rise in the blood pressure which persisted for several minutes and then returned to the basal hypertensive level. The normotensive patients also exhibited a pressor response, but the magnitude and duration of the blood pressure elevation was considerably less than that of the hypertensives receiving the same amount of l-dopa. The similarity of the l-dopa response in humans with essential hypertension and in hypertensive cats points to the possibility of a similar underlying

mechanism. The marked blood pressure rise in the human hypertensives may have resulted from defective renal deaminization due to inadequate arterial blood supply of the kidney parenchyma. Findings indicative of relative renal ischemia in human essential hypertension have been obtained by Goldring, Chasis, Ranges and Smith.[4] Similar evidence of diminished effective blood flow per unit of functioning tubular mass has also been demonstrated by Corcoran and Page,[5] for some but not all patients with essential and malignant hypertension.

From the experiments performed it appears that the pressor response is elicited only after a certain threshold value for l-dopa, and therefore of pressor amine, is reached. Blood pressure elevations were not observed with injections of less than 120 mg of dopa. However, it may well be that the maximum extent of the response during a given period of time may be limited, *i.e.*, after the maximum response has been obtained a greater rise need not necessarily occur with increasing amounts of l-dopa. This is illustrated in the experimental animal. A second injection of l-dopa caused no further augmentation of blood pressure when given during the maximum rise produced by the first injection. This may have been due to an inability of the decarboxylase to produce additional pressor amine during the given period of time, or if more hydroxytyramine were formed, to the fact that a plateau in the blood pressure response had already been reached.[6] The failure of small amounts of l-dopa to cause a blood pressure rise in the 2 patients with marked hypertension may be explained on the same basis. However, the amount of l-dopa given may have been too little to elicit a pressor response. It was considered inadvisable to expose these patients to the possible risk of larger amounts of l-dopa.

Summary. Peripheral intravenous injection of l-dopa was found to produce a marked rise in blood pressure in cats with experimental hypertension; no rise was produced in cats with acute renal ischemia or in normal cats. Intravenous injection of l-dopa in humans with essential hypertension produced a similar pressor response; a much less marked pressor effect was obtained in humans with normal blood pressure. The possibility is discussed of defective renal deaminization due to kidney ischemia as being responsible for the marked pressor response to l-dopa injections in essential human hypertension.

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4 Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W., *J. Am. Invest.*, 1941, **20**, 637.

5 Corcoran, A. C., and Page, I. H., *Proc. Am. Physiol. Soc.*, 1942, **1**, 17.

6 Ansari, M. Y., *Quart. J. Exp. Physiol.*, 1942, **31**, 161.