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Tyrosine administration reduces blood pressure and enhances brain norepinephrine release in spontaneously hypertensive rats

(methoxyhydroxyphenylethylglycol sulfate)

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ABSTRACT **Administration of L-tyrosine to normotensive or spontaneously hypertensive rats reduces blood pressure. The effect is maximal within 2 hr of injection. In spontaneously hypertensive rats, a dose of 50 mg/kg, intraperitoneally, reduces blood pressure by about 12 mm Hg (1 mm Hg = 1.33×10^2 pascals); a dose of 200 mg/kg produces the maximal effect, a reduction of about 40 mm Hg. Tryptophan injection (225 mg/kg) also lowers blood pressure in spontaneously hypertensive rats, but only by about half as much as an equivalent dose of tyrosine. Other amino acids tested (leucine, isoleucine, valine, alanine, arginine, and aspartate) do not affect blood pressure. Tyrosine injection appears to reduce blood pressure via an action within the central nervous system, since the effect can be blocked by co-administering other large neutral amino acids that reduce tyrosine's uptake into the brain. That tyrosine's antihypertensive action is mediated by an acceleration in norepinephrine or epinephrine release within the central nervous system is suggested by the concurrent increase that its injection produces in brain levels of methoxyhydroxyphenylethylglycol sulfate.**

Norepinephrine (NE) and possibly epinephrine release by nerve terminals in the mammalian central nervous system (CNS) modifies blood pressure. Depending on the locus, NE release can either increase or decrease blood pressure (1, 2). In the brain stem, stimulation of α-adrenergic receptors lowers blood pressure. The antihypertensive action of several drugs (e.g., clonidine and methyldopa) has been attributed to their ability to stimulate these brain-stem receptors (1). Epinephrine-containing neurons are also present in brain-stem regions involved in blood pressure regulation (3, 4). Thus, they may release their transmitter onto these same α receptors and thereby influence blood pressure.

The synthesis and release of NE (or possibly epinephrine) in the rat brain are influenced by the availability of the precursor amino acid, tyrosine. Thus, tyrosine administration, which raises brain tyrosine levels, stimulates dopa accumulation in rats pretreated with R04-4602 (an inhibitor of aromatic L-amino-acid decarboxylase); the injection of other large neutral amino acids, which lowers brain tyrosine levels, diminishes dopa formation (5–7). Tyrosine injection also increases brain levels of methoxyhydroxyphenylethylglycol sulfate (MOPEG-SO_4; ref. 8), indicating that NE and epinephrine release might be enhanced by precursor administration. If stimulation of central α receptors can lower blood pressure and if tyrosine administration does enhance the release of NE (or perhaps epinephrine) from CNS nerve terminals, then tyrosine injection might also lower blood pressure. The studies described below have tested this hypothesis.

METHODS

Male spontaneously hypertensive (SHR) rats of the Okamoto strain and normotensive Sprague–Dawley rats were obtained from Charles River Breeding Laboratories. They were housed two per cage, provided with food (Charles River Rat, Mouse, and Hamster Maintenance Formula) and water ad lib and exposed to light for 12 hr each day (Vita lite, 300 $\mu W/cm^2$; Duro-Test Corp., North Bergen, NJ).

The animals were used in experiments when their weights were between 250 and 350 g. Resting blood pressures in these animals were 170–210 mm Hg in SHR rats and 100–130 mm Hg in normotensive rats (1 mm Hg = 1.33×10^2 pascals). Arterial blood pressure was estimated by the tail-cuff method (9), with a pneumatic pulse transducer (Narco-Biosystems, Houston, TX). Animals were warmed at 37°C for 20 min prior to each reading; eight measurements were then made at each time point and the averaged value was taken as the blood pressure. Prior to use in an experiment, all animals were acclimated to this procedure for 4 days in order to minimize stress-induced fluctuations in blood pressure. When rats were used in more than one study, at least 7 days elapsed between experiments.

MOPEG-SO_4 levels were measured fluorimetrically (10) after isolation of the metabolite on QAE-Sephadex columns. Serum and brain tyrosine levels were also estimated fluorimetrically by the method of Waalkes and Udenfriend (11).

Amino acids (L-form, free base; obtained from standard commercial suppliers), dissolved or suspended in water immediately before use, were injected intraperitoneally (i.p.) in a volume of 2 ml/kg. Solutions were adjusted to pH 7 before injection. In some experiments, equimolar doses of tyrosine's highly soluble methylester hydrochloride (Aldrich) were used in lieu of tyrosine. However, tyrosine and its methylester were equally potent in reducing blood pressure.

RESULTS

Effect of Tyrosine Injection on Blood Pressure in Normotensive and SHR Rats. The i.p. injection of a large dose of L-tyrosine (400 mg/kg) into normotensive rats caused a small (-8 ± 1.5 mm Hg) but statistically significant fall in blood pressure (Fig. 1). Administration of the same dose to SHR rats dramatically reduced blood pressure for periods up to 4–5 hr (Fig. 2). The maximal effect, a fall of 40 ± 6 mm Hg, was observed within 2 hr (see Fig. 2). The tyrosine-induced decrease in blood pressure in SHR rats was dose dependent (Fig. 3):

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Abbreviations: SHR, spontaneously hypertensive; NE, norepinephrine; CNS, central nervous system; MOPEG-SO_4, methoxyhydroxyphenylethylglycol sulfate; i.p., intraperitoneal(ly).

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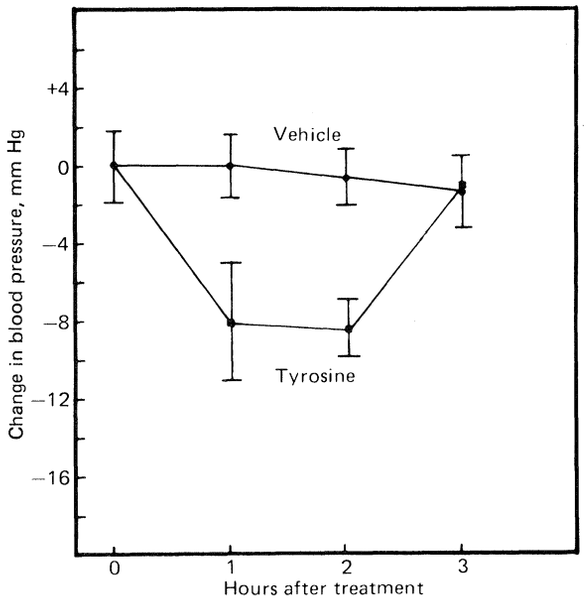

FIG. 1. Hypotensive action of tyrosine in normotensive rats. Tyrosine (400 mg/kg) or vehicle was administered i.p. to groups of six normotensive rats; blood pressures were measured immediately before injection and then at 1-hr intervals afterwards. Data are presented as the decreases in blood pressure from base line values (mean ± SEM). At 1 and 2 hr, but not at 3 hr, tyrosine treatment caused a significant decrease in blood pressure ($P < 0.05$). Data were analyzed by two-way analysis of variance and the Newman–Keuls test for the tyrosine group.

maximal effects were attained at a dose of 200 mg/kg. Although the dose of 50 mg/kg caused some reduction in pressure, 100 mg/kg was the smallest dose of tyrosine that consistently produced a significant fall in blood pressure.

Effects of Other Amino Acids on Blood Pressure in SHR Rats. Injection of leucine, isoleucine, valine, alanine, arginine, or aspartate (1.1 mmol/kg, equivalent to 200 mg/kg of tyrosine)

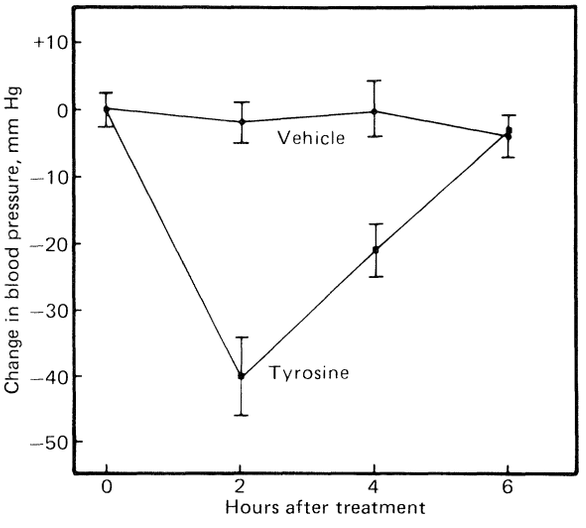

FIG 2. Time-course of the antihypertensive effect of tyrosine injection in SHR rats. Tyrosine (200 mg/kg) or vehicle was administered i.p. to groups of six SHR rats. Blood pressures were measured just prior to treatment, and then at 2-hr intervals afterwards. Data are expressed as the change in blood pressure from base line values (mean ± SEM). The antihypertensive effect of tyrosine was significant ($P < 0.01$) at 2 and 4 hr. Data were analyzed by two-way analysis of variance and the Newman–Keuls test for the tyrosine group.

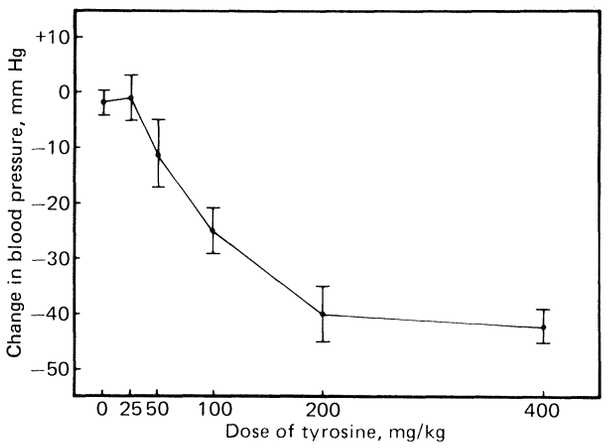

FIG. 3. Relationship between dose of tyrosine methylester and antihypertensive response in SHR rats. Tyrosine methylester, in doses equimolar to those of tyrosine indicated on the abscissa, was administered to groups of four SHR rats. Blood pressures were measured just before treatment and then 1.5 hr later. Data are expressed as the change from base line (mean ± SEM). The 100 mg/kg dose and each of the larger doses produced a significant decrease in blood pressure ($P < 0.01$). Data were analyzed by one-way analysis of variance and the Newman–Keuls test.

had no effect on blood pressure (Table 1). Tryptophan administration, however, did reduce blood pressure significantly, by about half as much as an equivalent dose of tyrosine.

Effect of Competing Amino Acids on Antihypertensive Action of Tyrosine in SHR Rats. To determine whether the antihypertensive action of tyrosine resulted from a direct effect on the CNS, we attempted to block the rise in brain tyrosine that follows its injection by coadministering valine or isoleucine. These compounds, like tyrosine, are large neutral amino acids and compete with tyrosine for uptake by the brain. Alanine was also tested as a control: it is not taken up into the brain by the carrier for tyrosine and thus does not suppress the rise in brain tyrosine after tyrosine administration. Coadministration of valine or isoleucine (0.55 mmol/kg) with an equimolar dose of tyrosine (100 mg/kg) blunted tyrosine's antihypertensive action; alanine failed to do so (Table 2 and Fig. 4). The injection of valine, isoleucine, or alanine alone (0.55 mmol/kg) did not affect blood pressure; however, a higher dose (3.88 mmol/kg) of valine alone caused a small increase in blood pressure (perhaps by diminishing brain tyrosine levels).

Table 1. Effects of amino acids on blood pressure in SHR rats

Amino acid	Change in blood pressure, mm Hg
Vehicle	1 ± 1
Leucine	−3 ± 2
Isoleucine	−2 ± 1
Valine	0 ± 1
Tyrosine	−46 ± 7*
Tryptophan	−27 ± 6*
Alanine	−2 ± 2
Aspartate	0 ± 2
Arginine	0 ± 3

Groups of four rats received tyrosine (200 mg/kg) or an equivalent dose (1.1 mmol/kg) of other amino acids i.p. Blood pressures were measured just before, and then 2 hr after, amino acid administration.

* $P < 0.05$ differs from vehicle group.

Table 2. Effects of isoleucine and alanine on antihypertensive action of tyrosine

Treatment	Change in blood pressure, mm Hg
Exp. 1	
Vehicle	−3 ± 3
Tyrosine	−38 ± 3*
Isoleucine	−5 ± 2
Tyrosine + isoleucine	−18 ± 8*†
Exp. 2	
Vehicle	−3 ± 2
Tyrosine	−28 ± 3*
Alanine	−2 ± 1
Tyrosine + alanine	−30 ± 6*

Groups of four SHR rats received (i.p.) vehicle, tyrosine (100 mg/kg; 0.55 mmol/kg), an equimolar dose of either isoleucine or alanine, or tyrosine along with either isoleucine or alanine. Blood pressures were measured just before treatment and 1 hr later.
* $P < 0.05$ differs from vehicle group.
† $P < 0.05$ differs from tyrosine group as well as vehicle group.

Effect of Tyrosine Injection on Brain MOPEG-SO_4 Levels in SHR Rats. Administration of an antihypertensive dose of tyrosine (200 mg/kg) to SHR rats increased whole-brain MOPEG-SO_4 levels ($P < 0.05$) both in animals subjected to (possibly stressful) blood pressure determinations and in rats used only for chemical measurements (i.e., no pressures taken; Table 3). The effect was maximal 30 min after tyrosine injection, but persisted for at least 4 hr.

DISCUSSION

These data show that doses of tyrosine that increase brain MOPEG-SO_4 levels (Table 3; ref. 8) also decrease blood pressure

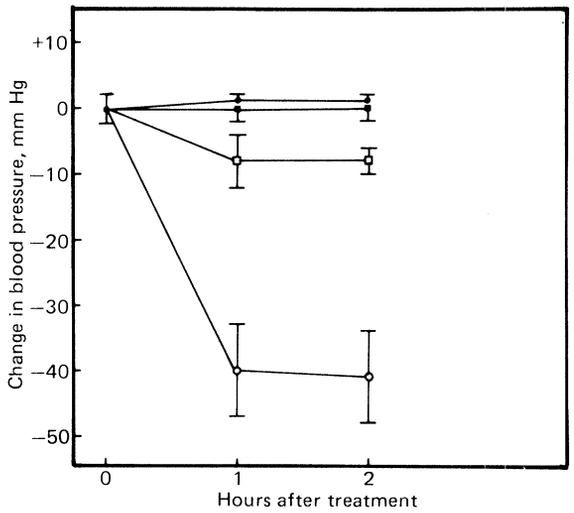

FIG. 4. Effect of valine on the antihypertensive action of tyrosine. Tyrosine (100 mg/kg; 0.55 mmol/kg) (○), valine (0.55 mmol/kg) (■), tyrosine plus valine (0.55 mmol/kg of each) (□), or vehicle (●) was administered to groups of four SHR rats. Blood pressures were measured just before treatment and then at 1-hr intervals afterwards. Data are expressed as the change in blood pressure from base line values (mean ± SEM). Tyrosine injection caused a significant fall in blood pressure ($P < 0.01$); treatment with tyrosine plus valine produced a slight decrease in blood pressure ($P < 0.05$), but this effect was not as great as that produced by tyrosine alone. Valine injection had no effect.

Table 3. Effect of tyrosine administration on serum tyrosine, brain tyrosine, and brain MOPEG-SO_4 in SHR rats

Time, min	Tyrosine: In serum, μg/ml	Tyrosine: In brain, μg/g	Brain MOPEG-SO_4, ng/g
0	14.6 ± 0.7	5.3 ± 0.2	104.7 ± 4.7
30	78.2 ± 2.1*	16.4 ± 1.7*	171.5 ± 15.8*
60	58.3 ± 3.1*	15.2 ± 2.8*	152.0 ± 6.0*
120	33.6 ± 1.1*	12.8 ± 0.3*	140.4 ± 5.7*
240	14.5 ± 0.5	5.8 ± 0.2	146.7 ± 7.8*

Groups of six SHR rats were injected i.p. with tyrosine methylester (235 mg/kg) and killed at the indicated times thereafter.
* $P < 0.05$ differs from time 0.

in normotensive and SHR rats (Figs. 1–4). The effective dose range, 50–200 mg/kg, is similar to that observed for another amino acid, methyldopa, used widely in the treatment of hypertension (12).

The temporal correspondence between the effects of tyrosine on blood pressure and on brain MOPEG-SO_4 levels in SHR rats is compatible with the view that the amino acid's antihypertensive effect results from stimulation of NE (or possibly epinephrine) release in the brain. Brain MOPEG-SO_4 levels have been reported to be a good index of NE release from nerve terminals (13). They might also reflect epinephrine release in brain regions that contain epinephrine-releasing neurons (3). Moreover, stimulation of α-adrenergic receptors in the brain stem has repeatedly been shown to lower arterial pressure (1). Additional evidence that the antihypertensive action of tyrosine involves release of catecholamines within the CNS is provided by the finding that the effect is blunted by coadministration of an amino acid (valine or isoleucine) that competes with tyrosine for brain uptake (14). (Injection of alanine, which does not compete with tyrosine for transport, is without effect.)

Two other reports have appeared suggesting that tyrosine administration can lower blood pressure. Osumi *et al.* (15) showed that blood pressure fell in SHR rats that consumed a diet supplemented with 1% L-tyrosine. The authors concluded, however, that the tyrosine effect "cannot be attributed to noradrenaline formed from tyrosine" (15). Shalita and Dikstein (16) suggested a possible false transmitter mechanism by which tyrosine might prevent the development of hypertension in rats treated with deoxycorticosterone acetate and salt. They proposed that the conversion of tyrosine to tyramine in the brain, with the subsequent displacement of NE from storage sites, could produce tyrosine's antihypertensive action. To support their hypothesis, they showed that the administration of D,L-tyrosine was more effective than administration of L-tyrosine in blocking hypertension caused by deoxycorticosterone acetate and salt. Since D-tyrosine can be converted to tyramine but not to NE, they reasoned that the enhanced antihypertensive action of the D,L-amino acid preparation probably resulted from the selective formation of tyramine from D-tyrosine. However, the brain uptake carrier for tyrosine is stereospecific for the L-isomer (14); therefore, if D-tyrosine does lower blood pressure, it probably does not do so via a central action unless it is first converted to L-tyrosine in peripheral tissues (17). Conceivably, if tyrosine administration led to tyramine accumulation in the periphery, blood pressure might ultimately be reduced if a false transmitter (such as octopamine) were stored in place of NE within sympathetic nerve terminals (18). However, the acute effect of circulating tyramine would be to increase blood pressure, not decrease it (see ref. 19). Hence, tyramine accumulation probably cannot account for the antihypertensive effect of tyrosine observed in the present studies.

The decrease in blood pressure induced by giving tryptophan

to SHR rats probably is mediated by an increase in the synthesis and release of serotonin from CNS neurons. Serotonin formation in the CNS is readily stimulated by tryptophan administration (20, 21), and treatments that increase serotonin turnover have been shown to reduce blood pressure (22, 23). In preliminary studies, we have found that pretreatment with a serotonin antagonist, metergoline, blocks the antihypertensive effect of tryptophan in SHR rats (unpublished observations). Because tryptophan and tyrosine compete for uptake into the CNS, the administration of one alone would act to decrease levels of the other. Therefore, perhaps simultaneous administration of both amino acids, rather than the administration of either amino acid alone, would be maximally effective in lowering blood pressure.

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