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Development of hypertension in spontaneously hypertensive rats fed L-tyrosine-supplemented diets

J. Bossy, R. Guidoux, H. Milon, and H. P. Würzner

Nestlé Research Department, CH-1814 La Tour-de-Peilz (Switzerland)

Summary

The blood pressure of spontaneously hypertensive rats (SHR) was measured by tail-plethysmography. Feeding SHR a diet supplemented with 0.6 g% L-tyrosine, for 15 weeks after weaning, resulted in a slower increase of blood pressure than in rats fed the control diet (no tyrosine added). The blood pressure stabilized, after about 8 weeks, at values lower by about 10 mm Hg than in the control SHR group. Diets with a higher content of free L-tyrosine (1.2 or 2.4 g%) produced no greater hypotensive effects, despite the fact that the plasma level of the amino acid, at the time of blood pressure measurements, was related to the tyrosine content of the diet. In addition, providing 2.4 g% free L-tyrosine to the diet of SHR with established hypertension, produced within a few days a decrease of blood pressure similar to the one recorded in rats fed the tyrosine-supplemented diet during the whole period of development of hypertension. A maximal effect of L-tyrosine, in decreasing the blood pressure of SHR, is thus obtained at relatively low concentrations of the amino acid in the diet, and after a short period of consumption. However, this effect is rather small, and rapidly reversed upon removing free L-tyrosine from the diet.

Zusammenfassung

Der Blutdruck von spontanen Hochdruck-Ratten (SHR) wurde durch Plethysmographie am Schwanz gemessen. Die Fütterung einer mit 0,6 g% L-Tyrosin supplementierten Futterration an SHR für 15 Wochen nach dem Absetzen ergab eine langsamere Zunahme des Blutdruckes im Vergleich zu Kontrollratten (ohne zugesetztes L-Tyrosin). Der Blutdruck stabilisierte sich nach ungefähr 8 Wochen mit Meßwerten, welche etwa 10 mm Hg tiefer lagen als in den Kontrollen. Futterrationen mit höheren Gehalten an L-Tyrosin (+1,2 und +2,4 g%) erzeugten keine weitere Blutdruckerniedrigung, obwohl das Plasmaniveau dieser Aminosäure zur Zeit der Blutdruckmessung dem Tyrosingehalt des Futters entsprach. In SHR mit ausgebildetem Hochdruck erniedrigte eine Futterration mit 2,4 g% freiem L-Tyrosin innerhalb weniger Tage den Blutdruck auf ein ähnliches Niveau wie in Ratten, welchen während der ganzen Versuchsperiode Tyrosin verabreicht wurde. Ein maximaler Effekt ist so schon mit relativ niedrigen Konzentrationen von L-Tyrosin nach kurzer Zeit der Verabreichung im Futter erreicht. Dieser Effekt ist jedoch ziemlich klein und verschwindet nach Einstellung der L-Tyrosin-Verabreichung rasch.

Key words: dietary L-tyrosine, blood pressure, SHR

Introduction

Hypertension is a serious health problem in many countries and is recognized as a substantial risk factor in the development of ischemic

heart disease and other cardio-vascular disorders. Despite considerable success in the treatment of hypertension with drugs, dietary therapy has found continuous interest and application.

Tyrosine was recently found to exert an acute and transient decrease of blood pressure in animals with different types of experimental hypertension (1, 7). In these studies, single doses of L-tyrosine were administered parenterally. In another study (5), a diet supplemented with 1 g% of L-tyrosine, fed to "spontaneously hypertensive rats" (SHR), was found to produce a slight decrease of blood pressure (by about 10 mm Hg) within 5 days. This effect remained stable during a two-week feeding trial.

The present investigations were designed to study the dependence of the hypotensive action of L-tyrosine, in SHR, on the tyrosine content of the diet and on the duration of its consumption. The diet was given *ad libitum* to young rats, for 15 weeks after weaning, so that its influence on the development of the hypertension could be assessed.

Material and methods

21-day-old male SHR were received from Iffa Credo, St-Germain-sur-l'Arbresle (France). The animals were specific pathogen-free (SPF) and were housed individually in type-III Macrolon cages with dust-free, autoclaved wood shaving Laborex (from Scierie "Les Eplatures", La Chaux-de-Fonds, Switzerland) in a barrier-sustained animal unit. Light was provided on a 12-hour day/night cycle (7 a.m. to 7 p.m.). The temperature was set at 23 °C ± 1 °, and humidity was kept at 55 % ± 5 %.

The basal control diet was laboratory chow Nafag 850 (Gossau, Switzerland), which contained 0.85 g% L-tyrosine (no free tyrosine), as determined by amino acid analysis (Durrum D 500) after acid hydrolysis. 4 groups of rats (15 rats in each group) were given diets supplemented with different amounts of L-tyrosine (0; 0.6; 1.2; and 2.4 g %). The diets were given from the 6th day after weaning, for a period of 15 weeks. The animals were given free access to food and sterilized drinking water. Food consumption and body weight were measured weekly.

Using a pneumatic pulse transducer, applied to the tail of the animal (Narco bio-systems Inc.), the systolic arterial pressure was measured in 10 rats of each group. The measurements were done in the morning, each rat being measured at 3-week intervals.

To avoid bias due to blood-pressure variations between and within days and to equalize time lapses between the last tyrosine consumption and measurements in each group, rats were selected for blood-pressure recording according to a preset alternating schedule.

The plasma level of L-tyrosine was measured in the remaining 5 rats of each treatment group at weeks 5, 11, 13, and 15. Blood sampling was done in the morning from the retro-orbital venous plexus, under slight CO_2/O_2 anesthesia. Plasma tyrosine was determined by UV absorption (280 nm) after separation by HLPC from protein-free plasma samples.

After 15 weeks, the diets were exchanged: the animals previously fed L-tyrosine-supplemented diets received the control diet, and those previously fed the control diet received the high-tyrosine diet (+ 2.4 g%). The study continued for a further 9-week period after crossing the diets.

Results

No side effect of L-tyrosine was observed, at any time and at any dose, and no difference in food consumption or body weight between rats fed

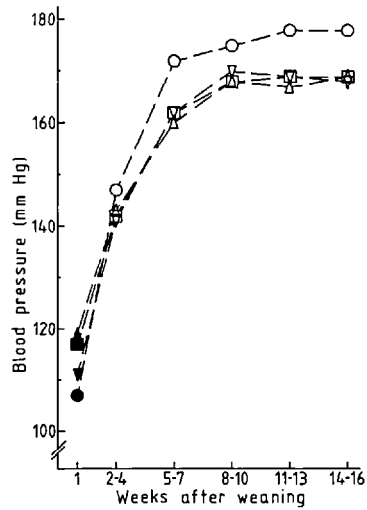

Fig. 1. Blood-pressure measurements in SHR fed diets supplemented with different amounts of L-tyrosine, from the first week after weaning. ●, ○: control diet (no tyrosine added). ▼, ▽: + 0.6 g% L-tyrosine. ▲, △: + 1.2 g% L-tyrosine. ■, □: + 2.4 g% L-tyrosine. Full marks show values obtained before adding L-tyrosine to the diet. Data are mean values from measurements in 10 rats.

the control diet and the experimental tyrosine-fed rats was noted during the study (not shown). When related to the weight of the animal, the amount of food (g/kg b.w. · day) and L-tyrosine ingested was about 3 times greater at the start than at the end (beyond the 12th week) of the study. During the first week, the mean intake of free tyrosine (added to the diet) ranged from 0.8 g/kg b.w. · day with the low-tyrosine diet (0.6 g%) to 3.6 g/kg b.w. · day with the high-tyrosine diet (2.4 g%).

From an early stage in the development of hypertension in the SHR, the blood pressure was lower in rats fed diets supplemented with L-tyrosine than in rats fed the control diet (fig. 1). Tyrosine was as effective at the low dose level (+ 0.6 g% in the diet) as at the high dose level (+ 2.4 g% in the

Table 1. Plasma concentrations of L-tyrosine in SHR fed diets supplemented with different levels of the amino acid. Measurements were done in rats fed the different diets for 7–15 weeks (8–16 weeks after weaning). Data are mean values (± 1 SEM) measured in 5 rats.

g% L-tyrosine added to the diet	Plasma L-tyrosine concentration (mmol/l) after				
	7 weeks	9 weeks	11 weeks	13 weeks	15 weeks
0 (Nafag only)	0.08 ± 0.006	0.10 ± 0.005	0.09 ± 0.005	0.10 ± 0.010	0.07 ± 0.005
0.6	0.11 ± 0.009	0.16 ± 0.006	0.13 ± 0.012	0.13 ± 0.006	0.10 ± 0.007
1.2	0.15 ± 0.011	0.19 ± 0.006	0.14 ± 0.017	0.15 ± 0.012	0.12 ± 0.007
2.4	0.25 ± 0.022	0.29 ± 0.007	0.17 ± 0.010	0.21 ± 0.022	0.19 ± 0.024

Table 2. Effect of exchanging the tyrosine-supplemented and -unsupplemented diets, given to the SHR, on blood pressure. The diets given to the rats were exchanged 16 weeks after weaning: rats previously fed the control diet, for 15 weeks, received the high tyrosine diet (+ 2.4 g%), while rats previously fed tyrosine-supplemented diets, for 15 weeks, received the control diet. All data are mean values (± 1 SEM) obtained from 10 rats.

Diet exchange (g% L-tyrosine added)	Blood pressure (mmHg) before exchange	after exchange 1–3 weeks	4–9 weeks
0 → 2.4	178 ± 0.7	169 ± 1.6	168 ± 0.8
0.6 → 0	168 ± 0.9	174 ± 2.4	176 ± 1.2
1.2 → 0	168 ± 0.9	175 ± 1.9	176 ± 0.8
2.4 → 0	169 ± 0.8	176 ± 1.3	177 ± 1.5

diet) in decreasing the blood pressure, which stabilized after 8 weeks at values lower by 9–11 mm Hg than in the control rats.

At the dose levels studied, the hypotensive effect of L-tyrosine was unrelated to the plasma concentration of the amino acid, which varied according to the tyrosine content of the diet (table 1).

Providing the high-tyrosine diet (+ 2.4 g%) to control group animals, at a stage of established hypertension (16th week), resulted in a rapid decrease of blood pressure. Blood pressure fell to values similar to the ones recorded in the groups of rats fed tyrosine-supplemented diets from the 2nd week after weaning. Conversely, removing free L-tyrosine from the diet of the latter groups of animals resulted in an increase of blood pressure to control values (table 2).

Discussion

The blood pressure of SHR fed diets supplemented with 0.6–2.4 g% L-tyrosine, from the 2nd week after weaning, rose to lower values than in rats fed the control diet. However, the hypotensive effect was slight, not larger than the one obtained by feeding older rats, with established hypertension, diets supplemented with 1 g% (5) or 2.4 g% L-tyrosine in our experiments. On the other hand, the effect of L-tyrosine on the blood pressure vanished rapidly upon removing the amino acid from the diet, even in rats fed the high-tyrosine diet for 15 weeks.

The fact that the hypotensive effect was independent of the amount of L-tyrosine added to the diet, above 0.6 g%, cannot be explained by a limitation of the rate of absorption of the amino acid from the gut, since the plasma concentrations of L-tyrosine, at the time of the blood pressure measurements, were found to vary according to the tyrosine content of the diet. The plasma concentration of L-tyrosine rose from about 0.1 mM under the low-tyrosine diet to 0.2–0.3 mM under the high-tyrosine diet.

According to several authors (2, 3, 8, 9), L-tyrosine has to cross the blood-brain barrier in order to exert its hypotensive action, which is mediated by a faster synthesis and release of catecholamines in some brain areas. However, the limitation of the hypotensive action of L-tyrosine, in our

experiments, could not be explained by saturation of the transport system for the amino acid at the blood brain barrier. As a matter of fact, increasing the serum level of the amino acid from 0.1 to 0.4 mM, by dietary manipulations in the rat, was found to produce related increases of both the rate of L-tyrosine influx into the brain and the brain level of the amino acid (2). A Km value for the transport of L-tyrosine across the blood-brain barrier was evaluated to 0.6 mM (6) in normal rats, and is not expected to be lower in SHR, since high blood pressures appear to favour the transfer of L-tyrosine from blood to brain (4). Our data suggest that the slight increment of the plasma level of the amino acid brought about by the low-tyrosine diet (+ 0.6 g%) was sufficient to make the brain level of L-tyrosine unlimiting, for the reaction catalysed by tyrosine hydroxylase, or high enough to ensure an ample supply of brain adrenergic transmitters mediating the hypotensive response. Since the tyrosine content of the control Nafag diet was evaluated to 0.85 g%, the diet content of L-tyrosine required to produce a maximal hypotensive effect, in SHR, should be comprised between 0.85 and 1.45 g%.

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Authors' address:

Dr. R. Guidoux, Research Department, Nestlé Products Technical Assistance Co Ltd, CH-1814 La Tour-de-Peilz (Switzerland)