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Effect of tryptophan and 5-hydroxytryptophan on the blood pressure of patients with mild to moderate hypertension

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Summary. Chronic treatment with L-tryptophan (4 g/day) reduced mean blood pressure in 8 of 9 patients with mild to moderate essential hypertension. No significant side effects of treatment were observed. An additional group of 8 patients was treated chronically with L-5-hydroxytryptophan (800 mg/day), the immediate precursor of serotonin. Five of the 8 patients had a significant reduction in mean arterial pressure. No significant side effects of treatment were observed. The reduction of blood pressure accompanying treatment with L-5-hydroxytryptophan suggests that at least a portion of the antihypertensive effect of L-tryptophan is mediated via serotonin.

Keywords: Amino acids – Essential hypertension – Blood pressure – L-Tryptophan – L-5-Hydroxytryptophan

Introduction

Chronic dietary treatment with the neutral amino acid, L-tryptophan, provides significant protection against the development of deoxycorticosterone acetate-salt-induced (DOCA) (Fregly and Fater, 1986; Fregly et al., 1987), Dahl salt sensitive (Lark et al., 1990), spontaneous (SHR) (Fregly et al., 1989), renal (Fregly et al., 1988a), and cold-induced (Riesselmann et al., 1991) hypertensions in rats. Chronic treatment with L-tryptophan has also been shown to reduce the elevated blood pressure of rats with established DOCA-induced hypertension (Fregly et al., 1988). In addition, patients with mild to moderate essential hypertension have also been treated successfully with L-tryptophan (Cade et al, 1990).

Tryptophan has three pathways by which it is metabolized in the body (Curzon and Knott, 1977). The major pathway, accounting for about 80% of the metabolism of tryptophan, is the kynurenine pathway. This is a multistep hepatic pathway whose end product is nicotinic acid (niacin). Nicotinic acid is important in the formation of several nucleotides, including nicotinic acid ribonucleotide and nicotinamide adenine dinucleotide (NAD). Earlier studies from this lab-

oratory showed that chronic dietary administration of nicotinic acid to rats provided significant protection against the development of DOCA-induced hypertension (Fregly et al, 1988b). In combination with tryptophan, it provided greater protection than either compound administered alone (Fregly et al, 1990). Thus, it is likely that intermediate metabolites in the kynurenine pathway may interact with tryptophan to prevent the development of hypertension.

A second pathway, accounting for about 2% of the metabolism of tryptophan, involves the formation of 5-hydroxytryptamine or serotonin. This occurs in certain specific tissues such as brain, gastrointestinal tract, and white cells of blood. This pathway appears to contribute to the antihypertensive effect of tryptophan since chronic treatment of rats with 5-hydroxytryptophan, the immediate precursor of serotonin, has been shown to prevent the elevation of blood pressure both in DOCA-treated (Fregly et al., 1987) and Dahl salt-sensitive (Baron et al, 1991) rats.

The third pathway, accounting for about 20% of the metabolism of tryptophan, is the formation of tryptamine. The potential role of this compound and its metabolites in any antihypertensive effect of tryptophan is unclear.

The results of earlier studies in humans with mild to moderate essential hypertension revealed that administration of L-tryptophan reduced blood pressure in 9 of 16 patients (Cade et al., 1990). In these patients, increasing doses varying from 1.5 to 4.0 g/day were administered for a total of 8 weeks. In the present studies, all patients were administered 4.0 g/day for varying periods of time. In addition, the effect of administration of L-5-hydroxytryptophan to other patients with mild to moderate essential hypertension was assessed.

Methods

Nine patients (6 male and 3 female), ranging in age from 34 to 64 years, with mild to moderate essential hypertension participated in the first study. Blood pressures (supine) were measured weekly for 4 weeks (control period) while the patients were off all medication. Upon admission to the study, medical histories and physical examinations were carried out on each of the patients. Blood pressure was measured in the supine position after 20 minutes of rest in a dimly lighted room by means of a mercury column sphygmomanometer. The fifth Karothoff sound was used as an approximation of diastolic pressure. In addition, a chest X-ray, a liver function test, complete hemogram (including hematocrit, hemoglobin, red and white cell counts, differential blood cell count), urinalysis, plasma creatinine concentration, creatinine clearance and a Zung Depression Test were carried out on each patient.

At the end of the control period, treatment with L-tryptophan (4 g/day, 1 g TID + hs) began. Each patient was generally seen at weekly intervals. The duration of treatment varied among patients from 6 to 16 weeks. Since all patients did not begin their treatment at the same time, the last patients to receive tryptophan had the shortest duration of treatment as a result of withdrawal of the compound from the market.

Eight patients (6 male and 2 female), ranging in age from 40 to 71 years, with mild to moderate essential hypertension participated in the second study. They underwent the same initial treatment and control period as described above for the first study. At the end of the control period, each patient was treated with L-5-hydroxytryptophan (800 mg/day, 200 g TID $\pm$ hs). Blood pressures were measured weekly thereafter as described in the first study. The duration of treatment varied from 6 to 20 weeks.

Statistical analysis of the data was carried out by means of a one-tailed t test and by linear regression analysis.

Results

Some characteristics of patients receiving L-tryptophan are shown in Table 1. Six of the nine patients were male and all were of the Caucasian race. The age range varied from 34 to 64 years. Body weights of the subjects did not change significantly during the course of treatment with tryptophan. The mean (±SE) initial pretreatment levels of systolic and diastolic blood pressure were 154 ± 4, and 101 ± 2 mm Hg, respectively. The mean (±SE) final levels of systolic and diastolic blood pressure were 142 ± 2, and 92 ± 2 mm Hg, respectively.

The responses of systolic and diastolic blood pressures to chronic treatment with tryptophan are shown in Fig. 1 and 2 for 6 of the 9 patients. In these cases, and in two others not shown, there was a significant reduction in mean blood pressure. In one patient shown in Figure 1B tryptophan was withdrawn for 2 weeks after which blood pressure was measured. A sharp increase in blood pressure occurred during the period of withdrawal from tryptophan. A significant ($P < 0.05$ to < 0.01) negative linear correlation coefficient was found for either systolic, diastolic, or both blood pressures during the course of treatment for 8 of the 9 patients (Table 1).

Some characteristics of patients receiving L-5-hydroxytryptophan are shown in Table 2. Six of the eight patients were male and all were of the Caucasian race. Age of the patients varied from 40 to 71 years. Mean body weight of the patients did not change significantly during the course of treatment. The initial mean (±SE) systolic and diastolic blood pressures were 158 ± 6 and 101 ± 2 mm Hg, respectively. The final mean (±SE) systolic and diastolic blood pressures were 145 ± 3 and 91 ±3 mm Hg, respectively.

The responses of systolic and diastolic blood pressure to treatment in 4 of the 8 patients are shown in Fig. 3. In these 4 patients, and in two others not shown, there was a significant reduction in mean blood pressure. A significant ($P < 0.05$ to < 0.01) negative linear correlation coefficient was found for either systolic, diastolic, or both blood pressures during the course of treatment for 5 of the 8 patients (Table 2).

The mean decrease in systolic and diastolic blood pressures from pretreatment control levels during the course of treatment with tryptophan and L-5-hydroxytryptophan are shown in Fig. 4. The mean decreases were virtually identical for the two compounds with tryptophan reducing systolic and diastolic blood pressures by 12 ± 3 and 9 ± 2 mm Hg, respectively, and L-5-hydroxytryptophan reducing blood pressures by 13 ± 5 and 11 ± 3 mm Hg, respectively. These reductions in blood pressure were significant in all cases.

Discussion

An earlier study in which 16 patients with mild to moderate essential hypertension were treated with L-tryptophan in gradually increasing doses revealed that 10 of the 16 patients had a significant reduction in mean arterial pressure (Cade et al, 1990). No significant side effects of treatment were observed.

In the present study, an additional 9 patients were treated chronically with L-tryptophan at the highest dose (4 g/day) used in the previous study. Eight of

Table 1. Some characteristics of patients receiving L-tryptophan (4 g/day)

Pt	M or F	Race	Age (yr)	Body Wt. (lb)		Recl. BP (mm Hg)				ΔBP (mm Hg)		Resp. to Trypt.*	
						Initial		Final					
				Init	Final	Sys.	Dias.	Sys.	Dias.	Syst.	Dias.	Syst.	Dias.
E.B.	F	W	50	148	148	154	103	152	88	−2	−15	−0.19	−0.82[b]
J.B.	M	W	54	165	166	148	103	142	96	−6	−7	−0.35	−0.59[a]
R.C.	M	W	61	202	204	156	96	140	82	−16	−14	−0.65[a]	−0.61[a]
B.T.	M	W	46	210	214	144	107	140	100	−4	−7	−0.62[a]	−0.97[b]
G.D.	M	W	53	265	269	136	98	135	93	−1	−5	−0.07	−0.69[a]
M.F.	M	W	64	185	187	181	100	152	90	−29	−10	−0.52[a]	−0.53[a]
C.M.	F	W	48	127	127	157	96	140	90	−17	−6	−0.08	−0.15
J.S.	M	W	49	248	250	162	110	142	96	−20	−14	−0.63[a]	−0.45
P.W.	F	W	34	205	203	145	97	132	94	−13	−3	−0.69[a]	−0.53[a]
Mean						154 ±4	101 ±2	142 ±2	92 ±2	−12 ±3	−9 ±2		

* Correlation coefficient: BP vs time
[a] Significant ($P < 0.05$)
[b] Significant ($P < 0.01$)

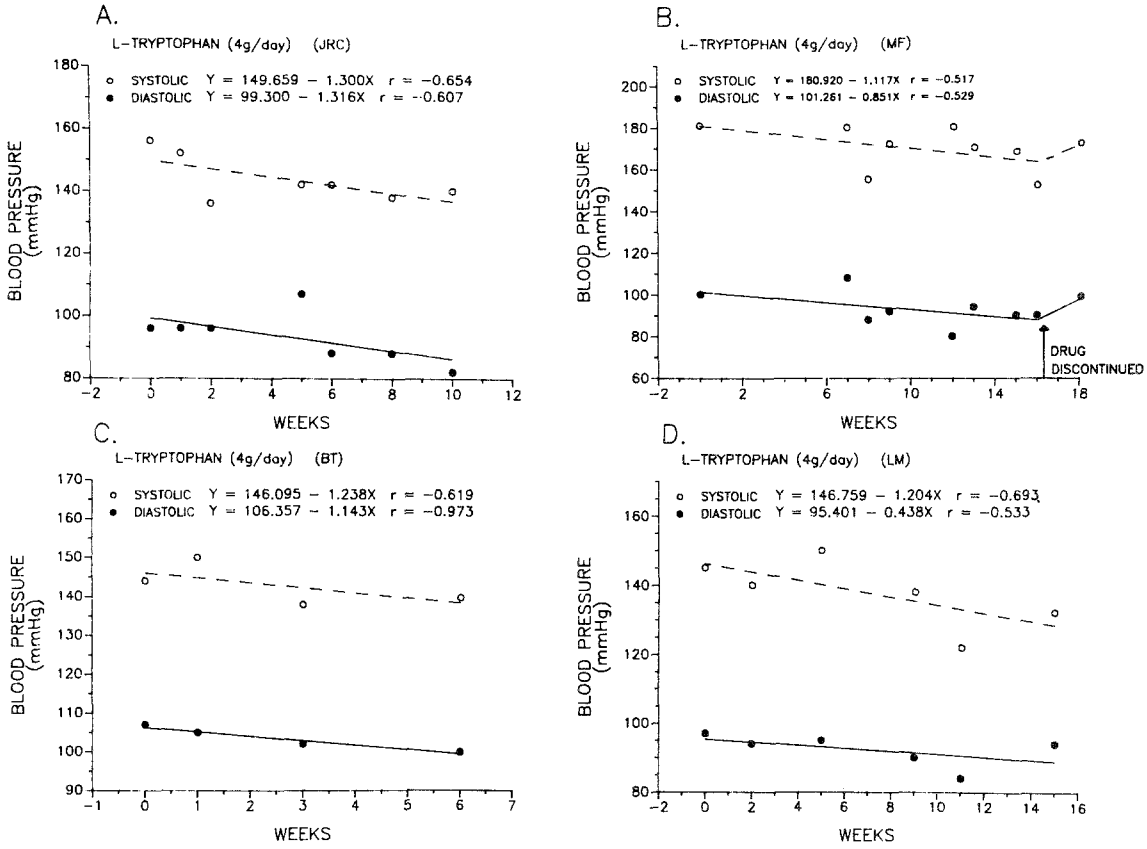

Fig. 1. Effect of chronic treatment of L-tryptophan (4 g/day) on systolic (open circle) and diastolic (closed circle) blood pressures of four patients. The regression equations and their correlation coefficients are shown for each patient. In patient MF (**B**) drug was withdrawn at the end of the sixteenth week

the patients had significant reductions in mean arterial pressure with no significant side effects noted. The results of these two studies suggest that humans with mild to moderate hypertension of unknown etiology may benefit from chronic treatment with L-tryptophan. These findings support the results of studies in rats in which renal (Fregly et al., 1988a), deoxycorticosterone acetate-induced (Fregly and Fater, 1986; Fregly et al., 1987), cold-induced (Riesselmann et al., 1991), spontaneously hypertensive (Fregly et al., 1989) and Dahl-salt sensitive hypertension (Lark et al., 1990) have either been prevented or ameliorated by chronic dietary treatment with tryptophan. Thus, it is quite clear that L-tryptophan has antihypertensive properties in both humans and rats. Important in this regard is the fact that tryptophan is a naturally occurring compound which had no significant side effects at the doses used in either the earlier or the present clinical study.

An additional group of 8 patients with mild to moderate hypertension of unknown origin was treated chronically with L-5-hydroxytryptophan (800 mg/day), the immediate precursor of 5-hydroxytryptamine or serotonin. Five of the 8 patients had a significant reduction in mean arterial pressure. No significant

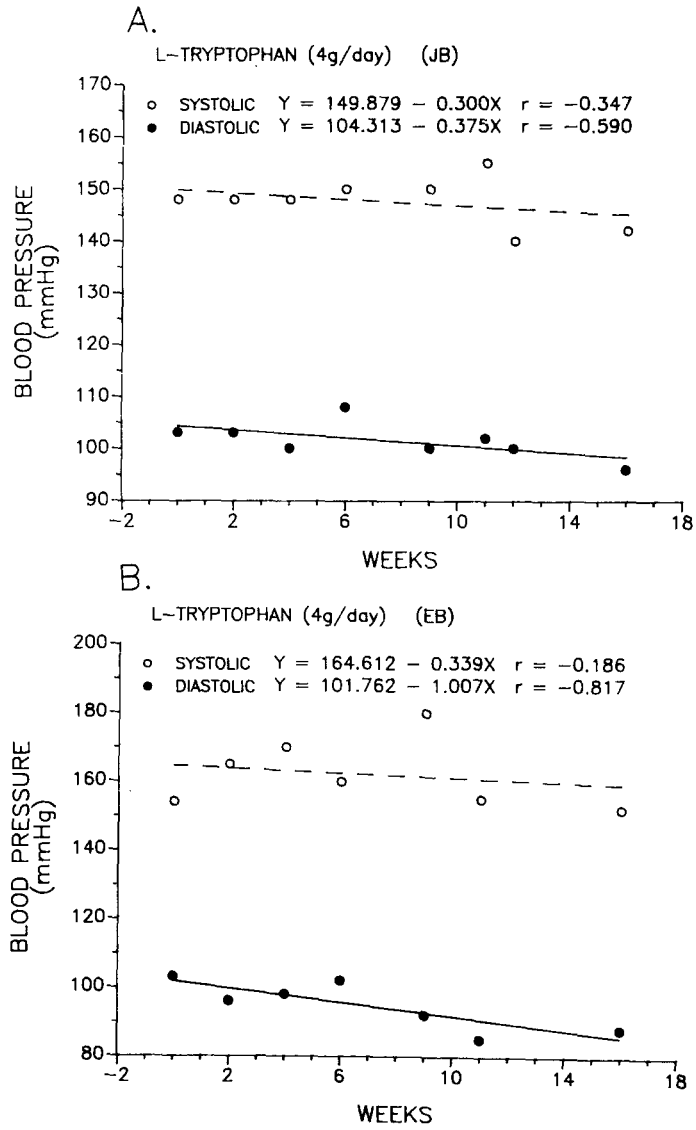

Fig. 2. Effect of chronic treatment with L-tryptophan (4 g/day) on systolic (open circle) and diastolic (closed circle) blood pressures of two patients. See legend of Fig. 1 for other details

side effects of treatment were reported by any of the patients. Although a smaller percentage of the patients receiving L-5-hydroxytryptophan responded positively to treatment than was the case for L-tryptophan (63 compared to 89%, respectively), both compounds reduced systolic and diastolic blood pressures by about the same amount (Fig. 4). Further, it must be kept in mind that only one dose of L-5-hydroxytryptophan was used in the present study. Hence, a possibility exists that a higher dose may have been more effective than the dose used here. This possibility awaits further study.

The antihypertensive effect of L-5-hydroxytryptophan is of particular interest since it suggests that at least a portion of the antihypertensive effect of tryptophan may be due to the formation of serotonin. The turnover of serotonin

Table 2. Some characteristics of patients receiving L-5-hydroxytryptophan (800 mg/day)

Pt	M or F	Race	Age (yr)	Body Wt. (lb)		Recl. BP (mm Hg)				ΔBP (mm Hg)		Resp. to Trypt.*	
						Initial		Final					
				Init	Final	Sys.	Dias.	Sys.	Dias.	Syst.	Dias.	Syst.	Dias.
M.A.	F	W	41	218	220	145	94	134	86	−11	−8	−0.48	−0.69[a]
M.D.	M	W	48	147	159	164	104	158	107	−6	+3	−0.60[b]	−0.09
S.J.	M	W	40	189	188	173	110	155	95	−18	−15	−0.43	−0.42
C.P.	M	W	71	229	230	151	98	145	88	−6	−10	−0.62[b]	−0.72[b]
D.S.	M	W	56	155	156	191	105	150	90	−41	−15	−0.86[b]	−0.87[b]
H.U.	M	W	68	165	164	160	106	140	84	−20	−22	−0.05	−0.37
S.B.	F	W	52	144	150	133	92	144	95	+11	+3	+0.15	−0.13
J.C.	M	W	60	190	191	149	102	135	80	−14	−22	−0.72[a]	−0.97[b]
Mean						158 ±6	101 ±2	145 ±3	91 ±3	−13 ±5	−11 ±3		

* Correlation coefficient: BP vs time
[a] Significant ($P < 0.05$)
[b] Significant ($P < 0.01$)

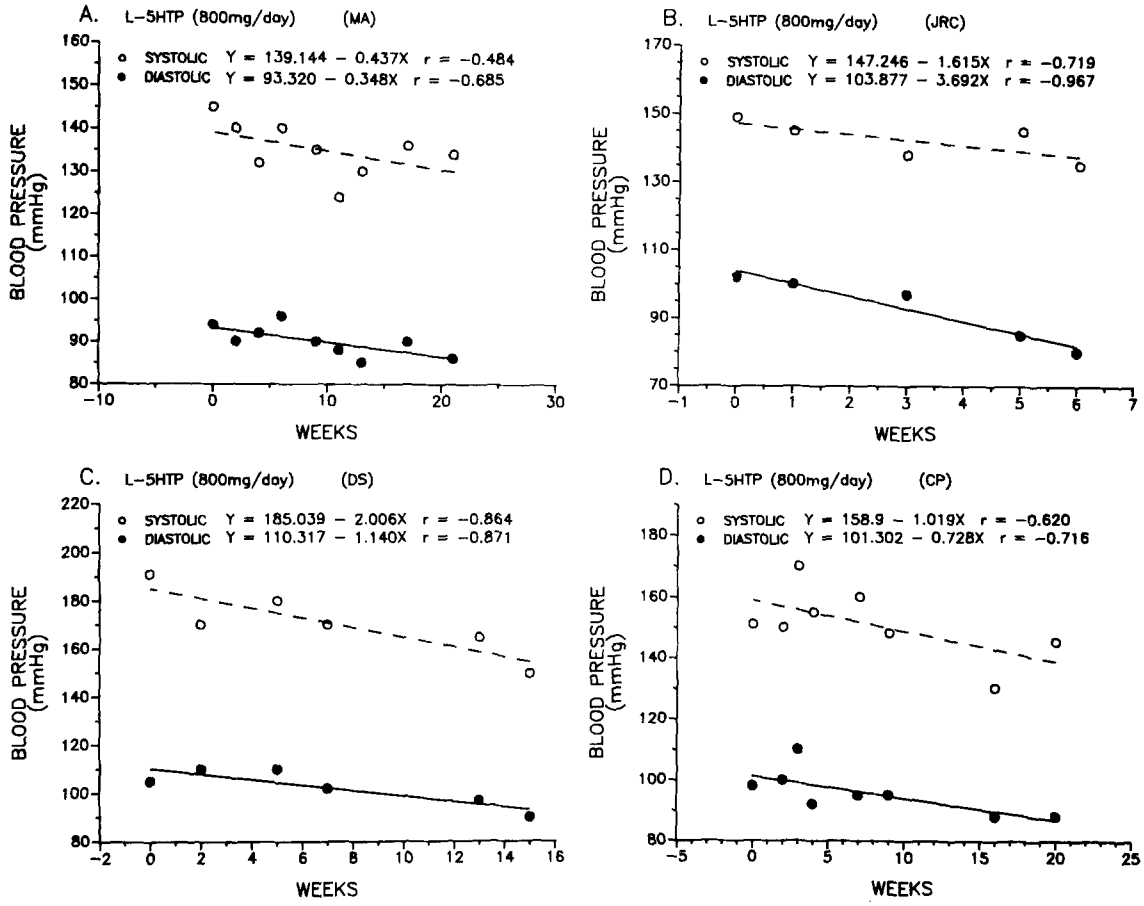

Fig. 3. Effect of chronic treatment of L-5-hydroxytryptophan on systolic (open circle) and diastolic (closed circle) blood pressures of four patients. The regression equations and their correlation coefficients are shown for each patient

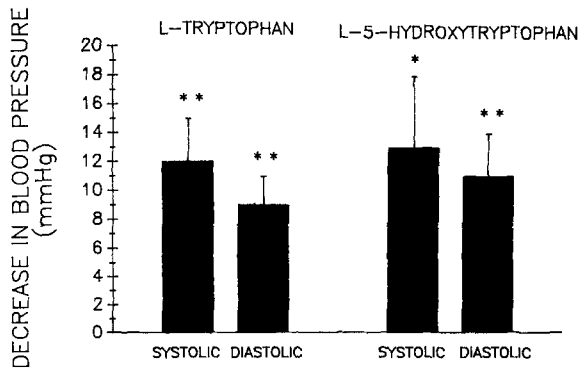

Fig. 4. The mean decrease in systolic and diastolic blood pressures of patients treated chronically with L-tryptophan and L-5-hydroxytryptophan is shown. One standard error is set off at each mean., * = $P < 0.05$; ** = $P < 0.01$ by one-tailed "t" test

in the brain of the rat has been shown to increase during chronic treatment with tryptophan (Fregly et al., 1987). However, the fewer apparent positive antihypertensive responses to 5-hydroxytryptophan than to tryptophan may be related to the fact that metabolites of tryptophan in the tryptamine and kynurenine metabolic pathways may also contribute to its antihypertensive effect. Indeed, we have reported that chronic treatment with nicotinic acid attenuated the development of hypertension in DOCA-treated rats (Fregly et al., 1988b). Further, treatment with a combination of tryptophan and nicotinic acid was more effective in preventing the elevation of blood pressure in DOCA-treated rats than treatment with either compound alone (Fregly et al., 1990).

The results of these studies in humans support the results of similar studies in rats in which DOCA-induced (Fregly et al, 1987) and Dahl salt sensitive (Baron et al, 1991) hypertensions have either been prevented or ameliorated by chronic treatment with 5-hydroxytryptophan. These results, taken together, support a role for serotonin in the development of all models of experimentally induced hypertension in which it has been tested.

With respect to the mechanism by which tryptophan and 5-hydroxytryptophan may mediate a reduction in blood pressure, recent evidence suggests that centrally produced serotonin may stimulate serotonergic receptors on spinal catecholaminergic neurons located in the descending bulbospinal pathways to induce vasodilation of peripheral resistance vessels and reduction of blood pressure (Ramirez et al, 1986). Teichbert et al. (1989) have also suggested that tryptophan can inhibit the transport of sodium across the wall of the gut. This could limit the amount of sodium absorbed and thus, in part at least, mediate the antihypertensive effect of tryptophan. Further, studies from this laboratory have shown that both tryptophan and 5-hydroxytryptophan reduce the number of binding sites for angiotensin II in the diencephalon of the brain (Fregly et al, 1987a; Fregly et al, 1987b). An increase in the number of these binding sites is associated with the development of DOCA-induced, spontaneously induced and Dahl salt sensitive hypertensions (Fregly et al, 1987a; Gutkind et al., 1988a,b; Plunkett and Saavedra, 1985).

Reduction of blood pressure in the patients participating in this study was not the result of a loss in body weight. As shown in Tables 1 and 2, body weights of both groups were relatively constant during the course of the studies.

While we have not tested whether patients with more severe hypertension would benefit from treatment with either tryptophan or 5-hydroxytryptophan, a clinical trial in which 5-hydroxytryptophan is administered alone, and in combination with other selected antihypertensive drugs, is in progress.

References

Baron A, Riesselmann A, Fregly MJ (1991) Pharmacology 42: 15–22
Cade JR, Fregly MJ, Privette M (1990) Amino acids-chemistry, biology and medicine. Escom Sci Publ, Leiden, pp 738–744
Curzon G, Knott PJ (1977) CRC Crit Rev Toxicol 5: 145–187
Fregly MJ, Fater DC (1986) Clin Exp Physiol Pharmacol 13: 767–776
Fregly MJ, Lockley OE, Cade JR (1988a) Pharmacology 36: 91–100
Fregly MJ, Lockley OE, Sumners C (1987a) J Hypertension 5: 621–628

Fregly MJ, Lockley OE, Torres JL, Cade JR (1988b) Pharmacology 37: 50–68
Fregly MJ, Lockley OE, van der Voort J, Sumners C, Henley WN (1987b) Can J Physiol Pharmacol 65: 753–764
Fregly MJ, Rudolph LW, Cade JR, Privette M (1990) Pharmacol (Life Sci Adv) 9: 441–445
Fregly MJ, Sumners C, Cade JR (1989) Can J Physiol Pharmacol 67: 656–662
Gutkind JS, Kurihara M, Castren E, Saavedra JM (1988a) J Hypertens 6: 79–84
Gutkind JS, Kurihara M, Castren E, Saavedra JM (1988b) Am J Physiol 255: H646–H650
Lark L, Witt P, Becker K, Studzinski W, Weyhenmeyer JA (1990) Clin Exp Hypertens A12: 1–13
Plunkett LM, Saavedra JM (1985) Proc Natl Acad Sci USA 82: 7721–7724
Ramirez AJ, Giarcovich SS, Enero MA (1986) J Hypertension 4 [Suppl 1]: S47–S49
Riesselmann A, Baron A, Fregly MJ (1991) Pharmacology (in press)
Teichberg S, Wapnir RA, Zdanowitz M, Roberts R, Ribeiro, H Jr, Lifshitz F (1989) Lab Invest 60: 88–101

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