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 Korothoff 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 + 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.