

Hypertension in Pyridoxine Deficiency

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Pyridoxal phosphate (PLP) is the coenzyme of various decarboxylases involved in the formation of monoamine neurotransmitters such as γ -aminobutyric acid (GABA), serotonin (5-HT) and dopamine. However, in the pyridoxine-deficient rats GABA and 5-HT are decreased in various brain areas including the hypothalamus, with no change in the catecholamine levels. Serotonin and GABA are known to be involved in blood pressure control mechanisms. In this study adult Sprague-Dawley rats placed on a pyridoxine-deficient diet for 8 weeks showed significant hypertension compared with pyridoxine-supplemented controls. This was associated with a general sympathetic stimulation. Treatment of deficient rats with a single dose of pyridoxine (10 mg/kg body weight) reversed the blood pressure to normal levels within 24 h, with concomitant restoration of hypothalamic 5-HT and GABA, as well as the return of plasma norepinephrine to normal levels. The results indicate that there is a cause-and-effect relationship between pyridoxine deficiency and hypertension.

Journal of Hypertension 1986, 4 (suppl 6):S174-S175

Keywords: Pyridoxine deficiency, serotonin, γ -aminobutyric acid, blood pressure.

Introduction

The crucial role played by pyridoxine in the nervous system is evident from the fact that the putative neurotransmitters are amines formed through decarboxylation of the precursor amino acid or amino acid derivative. We have reported a decrease in the brain levels of γ -aminobutyric acid [1] and serotonin, with no change in the levels of the catecholamines [2]. Non-parallel changes in serotonin and dopamine are related to the heterogeneity of the decarboxylases for 5-hydroxytryptophan and dihydroxyphenylalanine [3]. Receptor, behavioural and sleep studies attest to the functional consequences of the decrease in serotonin and γ -aminobutyric acid in various areas in the rat brain, including the hypothalamus [4-6]. We have also demonstrated the hypothalamic origin of hypothyroidism in the pyridoxine-deficient rat [7]. Various reports have indicated a relationship between pyridoxine status and blood pressure in pregnant women and women on anovulatory steroids. In view of the neurotransmitter and hormonal changes seen in pyridoxine deficiency we investigated the possibility that pyridoxine deficiency might lead to hypertension in non-pregnant mammals.

Methods and results

Adult male Sprague-Dawley rats (aged 6 weeks, 145 ± 8 g) used in these experiments were divided randomly into three groups, group 1 was placed on laboratory chow *ad libitum*, group 2 on pyridoxine-supplemented (control) diet and group 3 on a pyridoxine-deficient diet *ad libitum*. The rats in group 2 were pair-fed with pyridoxine-deficient rats. Systolic blood pressure was recorded weekly via tail-cuff plethysmography. At the end of the 8-week experimental period rats in all three groups were subdivided into two groups. One subgroup was injected with pyridoxine (10 mg/kg body weight i.p.) and the other with saline. Systolic blood pressures were recorded after 24 h. The data were analysed statistically by analysis of variance followed by Duncan's new multiple range test.

The mean body weights of normal, control and pyridoxine-deficient rats are as shown in Table 1. There was a significant decrease in body weight of both control and pyridoxine-deficient rats compared with the normal *ad libitum* fed rats. There was a significant increase in the systolic blood pressure in the pyridoxine-deficient group of animals compared with all the other groups

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Sponsorship: This study was supported by grants from The Manitoba Heart Foundation.

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1. Effect of pyridoxine status on systolic blood pressure of normal, control and pyridoxine deficient adult rats.

Animal status	Weight of rats (g)	Systolic blood pressure (mmHg)
Group 1, normal	425 ± 15	108 ± 3
Group 2, normal, Pyridoxine injected	436 ± 18	114 ± 4
Group 3, pyridoxine-supplemented (control)	265 ± 22	119 ± 3
Group 4, Control, Pyridoxine injected	251 ± 19	114 ± 4
Group 5, pyridoxine-deficient	206 ± 16	144 ± 4*
Group 6, pyridoxine-deficient, Pyridoxine injected	203 ± 20	108 ± 8

Values are means ± s.e.m. of eight to twelve animals in each group. * $P < 0.01$ compared with groups 1, 2, 3, 4 and 6, respectively (Duncan's multiple range test).

(Table 1). This increase in blood pressure was reversed to normal levels within 24 h of treatment with pyridoxine. Similar pyridoxine treatment of the normal and control rats did not result in any significant change in blood pressure values.

We also investigated the possibility that the reversible hypertension seen in deficient rats is related to general sympathetic stimulation in these animals. The concentration of norepinephrine in peripheral plasma can be taken as reflecting sympathetic activity validly [8]. Hence, blood samples were obtained from conscious rats without trauma through vascular-access-ports implanted in these rats. There was a significant increase in serum norepinephrine in the deficient group, indicating general sympathetic stimulation. Treatment of deficient rats with pyridoxine restored systolic blood pressure, serum norepinephrine and hypothalamic 5-HT and GABA to normal levels within 24 h, at a time when the plasma renin activity of the pyridoxine-deficient rat was still elevated, excluding a primary renal cause of the hypertension. Among the mechanisms to be considered for the hypertension seen in pyridoxine deficiency are the roles of serotonin [9] and GABA [10] in central regulation of blood pressure. Hypothyroidism is also known to cause hypertension, although the mechanism of this effect is not known [11].

Various hypertensive states share as a common feature an increased sympathetic outflow. In spite of the controversy regarding the central pressor or depressor effects of serotonin, a relationship between serotonergic transmission and tonic sympathetic outflow is indicated [12]. Hypertension induced by *p*-chlorophenylalanine in the rat is reversed by 5-hydroxytryptophan. This is blocked by transection of the brain-stem. It has been suggested that the primary effect of serotonin responsible for its depressor effect is the stimulation of the caudal brain-stem, which in turn depresses tonic sympathetic outflow [13]. Various studies using GABA, its agonists and antagonists also suggest a central GABA-ergic transmission of hypotensive effects [14,15]. Thus, decreased serotonergic and GABA-ergic central neurotransmission in the pyridoxine-deficient rat, acting through stimulation of sympathetic outflow, could cause the reversible hypertension in this animal model.

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