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REVERSIBLE SUPPRESSION OF NITRIC OXIDE SYSTEM IN ESSENTIAL HYPERTENSION

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ABSTRACT

Despite enormous research in the field of hypertension, its pathophysiology still remains largely unresolved and appears to be multifactorial. In the present communication, we have analyzed the status of nitric oxide (NO) in the patients with essential hypertension and age matched controls. We have found that the levels of NO are lowered in essential hypertension. The normalization of blood pressure by administration of antihypertensive therapy causes rise in the NO level indicating that perturbed NO status in essential hypertension is reversible. Addition of antioxidant to the antihypertensive drugs causes a further, though non significant, rise in the levels of NO, suggesting that antioxidants may be combined with antihypertensive drugs as adjunct in the management of essential hypertension.

KEY WORDS

Nitric oxide, Essential hypertension, Antihypertensive treatment, Antioxidants.

INTRODUCTION

As much as 95 % of hypertension is of unknown cause. The hemodynamic hallmark of primary hypertension, a persistently elevated vascular resistance, may be reached through a number of different paths. Before the final destination, these paths may converge and lead to thickening and constriction of vessel wall.

Vascular endothelium is not simply an inert blood container but has important regulatory role to prevent adhesion and aggregation of blood cells and keep the vessel dilated to the flow. One of the most potent substances released from the endothelium is nitric oxide(NO) (1). Recently, various NO system perturbations, including increased decomposition by superoxide ions, have been demonstrated and linked to pathogenesis of primary hypertension (2-6). The present communication evaluates NO status in essential hypertension (EH) and effect of antihypertensive and antioxidant therapies on it.

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MATERIALS AND METHODS

A total of 44 subjects were taken for the study. They included 15 age and sex matched healthy controls and 29 patients of uncomplicated essential hypertension. A detailed clinical examination of all the patients was done to detect target organ damage and coexisting other disorders. Hypertensives with cerebrovascular accidents, diabetes mellitus, coronary artery disease and renal failure were excluded from the study. All the cases were subjected to routine investigations eg. hematocrit, urine analysis and blood chemistry (urea, creatinine, lipids, sugar, Na^+ and K^+) and electrocardiogram. The hypertensives were randomized in two group. One group received only routine antihypertensive drug in a dose and till the time to bring the blood pressure within the normal range and the other group received the same antihypertensive drug along with 400 IU of vitamin E daily. The NO levels were monitored in all the cases before and after the treatment.

COLLECTION OF BLOOD

5 ml venous blood was drawn in disposable plastic syringe containing 0.5 ml of 3.8 % (w/v) solution of sodium citrate. Samples were immediately centrifuged at 800xg for 10 minutes and the supernatant plasma transferred in to plastic tubes and processed for NO estimation.

ESTIMATION OF NO

Indirect method of NO measurement, using Greiss reagent, as described by Privat *et al* (1977) (7) has been employed.

To 50 μl of serum, 48 μmole NADPH, 3 units of nitrate reductase and phosphate buffer (0.2M, pH 7.5) to make up the final volume to 100 μl were added. The reaction mixture was incubated at 30°C for 30 minutes. The reaction was set up in 96 well flat bottomed micro titre plates. The controls without serum and the standard with 2mM sodium nitrate were run simultaneously with each batch of assay. After incubation, 100 μl of freshly prepared Greiss reagent was added in each well.

The reaction mixtures were left at 30° C for at least 20 minutes then the plates were read at 550 nm. Concentrations in the samples were calculated by comparing the absorbances with the standard.

RESULTS

We have found significantly reduced levels of NO in the patients of essential hypertension compared to healthy controls ($p< 0.001$). Therapeutic restoration of blood pressure to normal value was associated with significant rise in NO levels in these patients ($p< 0.001$). Though the hypertensives, receiving anti-hypertensive drugs along with vitamin E, exhibited higher levels of NO after control of blood pressure than those receiving anti-hypertensive drug alone, but the difference was not found to be statistically significant ($p> 0.05$). The present report, thus, demonstrates that NO levels are reduced in essential hyper- tension and therapeutic control of blood pressure is associated with restoration back of the NO levels. This suggests that the perturbations in the NO system in hypertension are reversible. Further more, addition of antioxidant (vitamin E, 400 IU daily) along with anti hypertensive therapy causes further, but statistically non significant, elevation of NO levels (Table 1).

DISCUSSION

Furchgott and Zawadzki (1980) showed that vasodilatory response to acetyl choline was abolished in nor epinephrine induced vascular constriction if the endothelial lining was rubbed off (8). This phenomenon was found to be due to absence of endothelial derived release factor (EDRF). EDRF was later identified as nitric oxide and now known to be potent endogenous vasodilator (9,10). Inhibition of NO synthesis is associated with rise in blood pressure (11). Experimental animals lacking in the gene for NO synthase have been found to be hypertensive and incorporation of this gene has reversed hypertension (12,13). Nitroprusside, that contributes NO, is the most potent anti-hypertensive drug (14). In the present study, an attempt has been made to analyze the levels of NO in human hyper-tension and also to assess the effect of anti oxidant (vitamin E) on the levels of NO as an adjunct to anti-hypertesive drugs. We have found that NO levels are depressed in the patients of essential hypertension and therapeutic control of blood pressure is associated with the restoration of NO levels in these patients. The perturbations in the NO system in essential hypertension (EH) are, therefore, reversible. Panza *et al* (15) reported that usual anti-hypertensive therapy does not restore the impaired NO response to acetyl choline. Our findings support the observations of Kumar and Das(16) who have reported that NO levels are low in uncontrolled EH and that the levels revert back to normal values following the control of blood pressure. In the present study, incorporation of an anti oxidant, vitamin E, in the daily dose of 400 IU along with anti-hypertensive drug, causes elevation of NO levels compared to group of patients receiving anti-hypertensive drug alone. High dose multiple anti-oxidant therapy along with anti-hypertensive drugs have been shown to increase the availability of NO, thus helping in the lowering of blood pressure. This suggests that inclusion of anti oxidants would potentiate anti-hypertensive therapy (17). Our observations with mono anti- oxidant therapy in the standard dose,however, are not in quite conformity with these observations.

At the present, it is uncertain as how the defect in NO system arises in human hypertension (18). Depressed NO level elevates blood pressure by causing alterations of vasodilatory properties of vessel wall as well as by impairment of renal hemodynamic and excretory functions (19,20). It can be concluded that NO status is depressed in essential hypertension and normalization of blood pressure is associated with restoration of normal NO levels, indicating that impaired NO status in hypertension is reversible. It can be hypothesized that intraluminal pressure damages the endothelium resulting in altered release of NO. Normalization of intraluminal pressure results in the improvement of endothelial function resulting in the normalization of NO levels. Addition of anti-oxidant drugs

cause further rise, though non significantly, in NO levels suggests that anti oxidants may be used as an adjunct to anti-hypertensive therapy in the management of essential hypertension.

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Table 1. NO levels in control and hypertensive patients

Group	Mean±S.D.	S.E.	't'	'p'
Control (n=15)	33.04±2.8	0.72		
Hypertensives (n=29,before control of BP)	18.59±7.46	1.18	4.73	<0.001
Hypertensives,Vit.E+AHT (n=11, after control of BP)	29.67±7.87	2.37	1.52	>0.05
Hypertensives with AHT (n=14, after control of BP)	25.0±1.84	1.84		

n=the number of cases investigated; S.D.= standard deviation; S.E.= standard error ;
AHT=anti hypertensive drug treatment; conc. of NO expressed in mMole.
Control of blood pressure was achieved in 25 of the total patients (n=25).

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