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Abstract

We have investigated the chronic effects of Ohta's Isan and its ingredients on blood pressure in normotensive and uninephrectomized rats. Ohta's Isan and sodium bicarbonate had no significant effect on blood pressure in normotensive rats. Sodium bicarbonate at a dose of 625 mg/kg/day accelerated a slow increase in blood pressure on uninephrectomized rats given 1% saline drinking water, while Ohta's Isan and its plant components had no influence on blood pressure. The plant components, as well as Ohta's Isan, inhibited an increase in blood pressure on uninephrectomized rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water, while antacids had no influence on blood pressure. These results elucidate that the chronic administration of Ohta's Isan may not be associated with the development of hypertension, but its plant components may play a role in protection against the aggravation of hypertension induced by sodium overload, in addition to the intended effects on the gastrointestinal tract.

Keywords: Ohta's Isan, plant components, sodium bicarbonate, blood pressure, uninephrectomized rats, antacid, hypertension.

Introduction

A trademark, Ohta's Isan, is a commercial stomachic mixture containing stomachic herbs, antacids, and digestants. Ohta's Isan, being derived from gastric medication which was prescribed by A.F. Bauduin, a Dutch doctor in the middle of 19th century, has been marketed for the treatment of a variety of

gastrointestinal disorders, such as hyperchlorohydria, stomachache, anorexia, gastric dyspepsia, abdominal distention, etc., in Japan. Recently, concern has been expressed whether the chronic effect of sodium bicarbonate, the major antacid contained in Ohta's Isan, might be associated with the development of hypertension, despite Ohta's Isan having been regularly used for the treatment of the afore mentioned disorders over many decades. It is well-known that a high dietary intake of sodium chloride is capable of inducing hypertension in humans and animals (Meneely & Ball, 1958; Dahl, 1977; Morgan et al., 1980). However, it is suggested that the hypertensive effects of sodium chloride were likely due to excess chloride intake rather than due to sodium overload, since it has been reported that sodium bicarbonate neither potentiated the hypertensive effects of deoxycorticosterone acetate (Kurtz & Morris, 1983) nor induced salt hypertension in Dahl salt-sensitive rats (Whitescarver et al., 1984). These findings can reduce anxiety about the effect of Ohta's Isan on the development of hypertension to some extent. On the other hand, Zicha et al. (1986) have reported that blood pressure was increased in uninephrectomized DOCA-treated rats which were fed a diet containing sodium bicarbonate or sodium chloride, as compared to rats fed a low-salt diet only. They have shown that DOCA-salt hypertension induced by feeding of sodium bicarbonate or sodium chloride diet was associated with an increase of systemic resistance caused by sodium overload. In order to clarify the disputed effect of Ohta's Isan and its ingredients on the development of hypertension, the present study was therefore designed to evaluate the chronic effects of Ohta's Isan and its ingredients on the

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alteration of blood pressure in normotensive and uninephrectomized rats.

Materials and methods

Drug preparations

Ohta's Isan was supplied from our factory. Ohta's Isan in a dosage of 1300 mg contained 625 mg sodium bicarbonate, 133 mg precipitated calcium carbonate, 26 mg magnesium carbonate, 273.4 mg synthetic aluminum silicate as antacids, 40 mg diastase as digestants, 92 mg cinnamon bark (*Cinnamomum cassia* Blume, Lauraceae), 24 mg fennel (*Foeniculum vulgare* Mill. Umbelliferae), 20 mg nutmeg (*Myristica fragrans* Houtt., Myristicaceae), 12 mg cloves (*Syzygium aromaticum* (L.) Merr. et L.M. Perry, Myrtaceae), 22 mg *Citrus unshiu* Marcow. peel, (Rutaceae) 15 mg gentian (*Gentiana lutea* L., Gentianaceae), 15 mg powdered picrasma wood (*Picrasma quassioides* Bennet, Simaroubaceae) as plant components and *l*-menthol as a corrigent.

Animals

Male Wistar rats weighing 140–150 g were obtained at 5 weeks of age from Japan SLC Co., Ltd. (Shizuoka, Japan). All animals were placed in cages and maintained in an airconditioned room with illumination from 7 a.m. to 7 p.m. The room temperature (22 ± 2 °C) and humidity ($55 \pm 10\%$) were controlled automatically. The laboratory chow (pellets) (Funabashi Nojo KK, Chiba, Japan) and water were given *ad libitum*. All animals were maintained for more than 1 week, prior to the experiment.

Chronic effects of Ohta's Isan and sodium bicarbonate on blood pressure in normotensive rats

Thirty rats whose systolic blood pressure was within the range from 80 to 120 mmHg, were divided into 5 groups, at the start of the experiments. The animals of the first group were taken as controls. The animals of 3 groups among the remaining 4 groups were administered orally Ohta's Isan suspension in 1% gum arabic solution 5 times a week, at doses of 325, 650 and 1300 mg/kg/day, respectively for 13 weeks. The animals of the remaining group were administered orally sodium bicarbonate suspension in 1% gum arabic solution 5 times a week, at a dose of 625 mg/kg/day for 13 weeks. Control rats were administered orally 1% gum arabic solution (5 mL/kg) as the vehicle. For the duration of the study, 6 animals were placed in each cage with water and food ad libitum. Systolic blood pressure was measured indirectly once a week in unanesthetized rats by the plethymographic tail-cuff technique using a rat tail manometer-tachometer system (UNICOM TK-350, MUROMACHI KIKAI Co., LTD. Japan). Prior to blood pressure determinations, the animals were maintained in an environment of 35 °C for 15 min. Each determination was averaged out from at least three readings.

Chronic effects of Ohta's Isan and its ingredients on blood pressure in uninephrectomized rats given 1% saline drinking water

All animals were uninephrectomized according to the method of Meneely et al. (1953). Briefly, a midline incision was made after the rat was anesthetized by inhalation of ether. The left kidney was exposed and removed after the vessel and ureter on the left side were ligated. The abdominal incision was closed by suturing and the rats were housed in cages for 1 week. The rats were divided into 4 groups at the start of the experiment. The animals of the first group were taken as controls. The animals of the second group were administered orally Ohta's Isan suspension in 1% gum arabic solution 5 times a week, at a dose of 1300 mg/kg/day for 12 weeks. The animals of the third group were administered orally its plant components including cinnamon bark, fennel, nutmeg, clove, citrus unshiu peel, gentian and powdered picrasma wood, suspended in 1% gum arabic solution, 5 times a week, at a dose of 200 mg/kg/day for 12 weeks. The animals of the fourth group were administered orally sodium bicarbonate suspension in 1% gum arabic solution 5 times a week, at a dose of 625 mg/kg/day for 12 weeks.

Control rats were administered orally 1% gum arabic solution (5 mL/kg) as the vehicle. For the duration of the study, 5 animals were placed in each cage with 1% saline drinking water and food *ad libitum*. The measurement of blood pressure was carried out in the same manner as described above.

Anti-hypertensive effects of Ohta's Isan and its ingredients on uninephrectomized hypertensive rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water

Unilateral nephrectomy of the rats was performed in the same manner as described above. One week later, the rats were fed with the powdered diet (Funabashi Nojo KK, Chiba, Japan) including 19.2 mg/1 g food of sodium bicarbonate and allowed free access to 1% saline drinking water for 5 weeks. During this time, the blood pressure of each rat was measured once a week. When the mean value of blood pressure reached 140 mmHg in the 5th week, the rats were divided into 4 groups. The first group continued to be fed with 19.2 mg/1g food of sodium bicarbonate diet. The second group was given 40 mg/1 g food of Ohta's Isan diet. The third group was given food into which 19.2 mg sodium bicarbonate and 6.15 mg plant components (2.83 mg cinnamon bark, 0.74 mg fennel, 0.62 mg nutmeg, 0.37 mg clove, 0.67 mg citrus unshiu peel, 0.46 mg gentian, 0.46 mg powdered picrasma wood) were mixed per 1 g food. The fourth group was given food into which 32.5 mg antacids (19.2 mg sodium bicarbonate, 4.09 mg precipitated calcium carbonate, 0.8 mg magnesium carbonate, 8.41 mg synthetic aluminum silicate) were included per 1g food. Seven animals were placed in each cage with 1% saline drinking water and each food ad libitum. The blood pressure of each rat was measured once a

week for the duration of the experiment. Food and water intake was also checked and sodium intake was calculated.

Statistical analysis

All data were expressed as the means \pm standard error of the mean (SEM). Significant differences were evaluated by oneway analysis of variance (ANOVA) and Dunnet's multiple range test.

Results

Chronic effects of Ohta's Isan and sodium bicarbonate on blood pressure in normotensive rats

The blood pressure measurements of the vehicle-treated rats were within the range from 95.68 to 108.22 mmHg for 13 weeks. As shown in Figure 1, Ohta's Isan at doses of 325 mg/kg/day, 650 mg/kg/day and 1300 mg/kg/day, respectively, showed no significant differences in blood pressure at the each week, as compared to the vehicle-treated group. Also, sodium bicarbonate had no influence on blood pressure. Over the entire course of the experiment, Ohta's Isan and sodium bicarbonate had no significant effect on blood pressure in normotensive rats.

Chronic effects of Ohta's Isan and its ingredients on blood pressure in uninephrectomized rats given 1% saline drinking water

As shown in Figure 2, the blood pressures of vehicle treated rats were within the range from 99.8 to 123.4 mmHg for 12 weeks, and some increase in blood pressure was shown in



Figure 1. Changes in systolic blood pressure in normotensive rats following chronic treatment with Ohta's Isan or sodium bicarbonate.

 $-\bigcirc -=$ vehicle treated group (n = 6); $-\bigtriangleup -= 325 \text{ mg/kg/day}$ of Ohta's Isan treated group (n = 6); $-\varkappa -= 650 \text{ mg/kg/day}$ of Ohta's Isan treated group (n = 6); $-\bigsqcup -= 1300 \text{ mg/kg/day}$ of Ohta's Isan treated group (n = 6); $-\boxdot = 625 \text{ mg/kg/day}$ of sodium bicarbonate treated group (n = 6).



Figure 2. Chronic effects of Ohta's Isan and its ingredients on blood pressure in uninephrectomized rats given 1% saline drinking water.

 $-\bigcirc -=$ vehicle treated group (n = 5); $-\bigtriangleup -= 1300 \text{ mg/kg/day}$ of Ohta's Isan treated group (n = 5); $-\varkappa -= 200 \text{ mg/kg/day}$ of plant components treated group (n = 5); $\cdots \blacksquare \cdots = 625 \text{ mg/kg/day}$ of sodium bicarbonate treated group (n = 6).

*p < 0.05; **p < 0.01 compared to vehicle treated group.

+p < 0.05; ++p < 0.01 compared to pretreatment value in each group.

uninephrectomized rats given 1% saline-drinking, as the experiment progressed. The hypertensive effects were significant at 4 and 6 weeks, in comparison with pretreatment. No significant differences were observed between Ohta's Isan treated group and vehicle treated group, although Ohta's Isan showed a significant increase of blood pressure in 3, 5, 6, 8 and 9 weeks, as compared to that in the pretreatment. Also, there were no significant differences in blood pressure between the plant components treated group and the vehicle treated group. However, the sodium bicarbonate treated group showed a significant increase in blood pressure on and after the 3 week, as compared to that in the pretreatment. Moreover, the hypertensive effects were significantly different at 5, 7, 8, 9, 11 and 12 weeks, in comparison with each blood pressure in the vehicle treated group. Therefore, sodium bicarbonate at a dose of 625 mg/kg/day increased the blood pressure in uninephrectomized rats given 1% saline drinking water, while Ohta's Isan and its plant components had no influence.

Anti-hypertensive effects of Ohta's Isan and its ingredients in uninephrectomized hypertensive rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water

As shown in Figure 3, when uninephrectomized rats were fed with the powdered diet including 19.2 mg/l g food sodium bicarbonate and allowed free access to 1% saline drinking water for 5 weeks, the blood pressure increased gradually, and reached $140.69 \pm 2.20 \text{ mmHg}$. The blood pressures in the sodium bicarbonate treated group at 6, 7 and 8 weeks, were $148.93 \pm 4.43 \text{ mmHg}$, $160.24 \pm 6.37 \text{ mmHg}$ and $160.96 \pm$



Figure 3. Anti-hypertensive effects of Ohta's Isan and its ingredients in uninephrectomized hypertensive rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water.

 $-\bigcirc -= 19.2 \text{ mg/g}$ food of dietary sodium bicarbonate pretreated group for 5 weeks (n = 28); $- \bigcirc -= 19.2 \text{ mg/g}$ food of dietary sodium bicarbonate treated group (n = 7); $-\blacktriangle -= 40 \text{ mg/g}$ food of dietary Ohta's Isan treated group (n = 7); $-\varkappa -= 19.2 \text{ mg}$ of sodium bicarbonate plus 6.15 mg of plant components per 1 g dietary treated group (n = 7); $-\blacksquare -= 32.5 \text{ mg/g}$ food of dietary antacid treated group (n = 7).

**p < 0.05; **p < 0.01; Significantly different from dietary sodium bicarbonate treated group.

5.45 mmHg, respectively. In the group that continued to be fed with 19.2 mg/1 g food of sodium bicarbonate diet, a still greater increase in blood pressure was observed. The blood pressures in the Ohta's Isan treated group at 6, 7 and 8 weeks were 147.57 ± 3.51 mmHg, 132.14 ± 4.05 mmHg and 127.13 \pm 4.78 mmHg, respectively, and a decrease in blood pressure was observed. The effects were significantly different at the 7 and 8 weeks, in comparison with those in the sodium bicarbonate treated group. The blood pressures in the plant components added group at 6, 7 and 8 weeks were 146.21 \pm 4.15 mmHg, $120.29 \pm 6.25 \text{ mmHg}$ and $115.37 \pm 4.11 \text{ mmHg}$, respectively, and it was observed that the addition of the plant components decreased the blood pressure. As well as Ohta's Isan treated group, the effects were significantly different at 7 and 8 weeks, as compared to those in the sodium bicarbonate treated group. Eventually, in both the Ohta's Isan treated group and the plant components added group, a pronounced depression of blood pressure was observed during the 2 weeks after treatment. In the case of the antacids, the blood pressures in the 6th, 7th and 8th weeks were $153.21 \pm$ 4.58 mmHg, $146.61 \pm 4.34 \text{ mmHg}$ and $147.36 \pm 5.29 \text{ mmHg}$, respectively. There was no significant difference in blood pressure between the antacids treated group and sodium bicarbonate treated group. When sodium intakes in the groups were calculated during three weeks after division, the cumulative sodium intakes per animal in the sodium bicarbonate treated group, Ohta's Isan treated group, plant components added group and antacids treated group, from the 6th week to 8th week, were 173.00 mEq, 166.82 mEq, 173.47

mEq and 175.23 mEq, respectively. Thus, little difference among the groups was observed for sodium intake.

Discussion

The present results indicate that chronic administration of Ohta's Isan and sodium bicarbonate had no influence on blood pressure in normotensive rats. Sodium bicarbonate at a dose of 625 mg/kg/day accelerate a slow increase of blood pressure in uninephrectomized rats given 1% saline drinking water, while Ohta's Isan including an equivalent amount of sodium bicarbonate had no significant effect on blood pressure. Meneely et al. (1953) have reported that sustained arterial hypertension developed in male albino rats chronically fed diets rich in sodium chloride with drinking water available ad libitum, and that a positive, linear correlation was found between the systolic blood pressure and the concentration of sodium chloride in the diet after 12 months of the experimental regimen. Their findings are nearly consistent with the increase of blood pressure in uninephrectomized rats given 1% saline drinking water in our observation, although the increase in blood pressure was gradual over the 12 weeks.

Kotchen et al. (1983) have reported that chloride induced hypertension, as a result of sodium chloride or selective chloride inhibited plasma renin activity. Also, Kurtz et al. (1987) demonstrate that the anion component of an orally administered sodium salt can influence the ability of that salt to increase blood pressure, in view of the fact that supplemental sodium chloride increased plasma volume and urinary excretion of calcium whereas sodium citrate did not, although both salts induced sodium retention, weight gain, and suppression of plasma renin activity and plasma aldosterone. Eventually, they suggest that the hypertensive effects of sodium chloride were likely due to excess chloride intake rather than due to sodium overload. However, our results indicate that sodium bicarbonate potentiated the increase of the blood pressure in uninephrectomized rats given 1% saline drinking water. These findings can not be attributed only to differences in bicarbonate or chloride anion, and it is suggested that the hypertensive effect of sodium chloride may be partially associated with sodium overload. Furthermore, our results suggest that Ohta's Isan and its plant components have no significant effect on blood pressure in uninephrectomized rats given 1% saline drinking water. Successively, it was investigated whether Ohta's Isan and its plant components might have a hypotensive effect on uninephrectomized hypertensive rats induced by sodium overload. The results indicated that both Ohta's Isan and its plant components had a hypotensive effect on uninephrectomized hypertensive rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water, whereas antacids had no influence. Moreover, there was very little difference in the sodium intake between groups. These results suggest that the plant components may be an effective constituent of Ohta's Isan

on blood pressure. It is known that some herbal medicines containing Ohta's Isan's plant components have a hypotensive effect. Harada and Yano (1975) have reported that cinnamaldehyde, the major component of Chinese cinnamon, exerted a fall in blood pressure with increasing respiratory rate and femoral blood flow in an anesthetized dog. Also, Kuang and Gu (1988) have reported that *Cinnamomum cassia* has a hypotensive effect on skelton hypertensive rats. Furthermore, Matsubara et al. (1985) have reported that six flavonoid glycosides isolated from *Citrus unshiu* peel have a depressive effect on blood pressure. From these findings taken together, it seems possible that cinnamon bark or *Citrus unshiu* peel in the plant components of Ohta's Isan may possibly have an influence on blood pressure in uninephrectomized rats given 1% saline drinking water.

In the present study, we found that Ohta's Isan has no influence on normotensive and uninephrectomized rats given 1% saline drinking water, and that Ohta's Isan and its plant components inhibited the increase of blood pressure on uninephrectomized rats chronically fed diets rich in sodium bicarbonate with 1% saline drinking water. When considered together, these results demonstrate that chronic administration of Ohta's Isan may not be associated with the aggravation of hypertension. Furthermore, the present study pharmacologically suggests that stomach herbs may play a role in protection against the aggravation of hypertension induced by sodium overload, in addition to the intended effects on the gastrointestinal tract. Further investigations need to be done to identify the effective constituents of the plant components.

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