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Acute Hypotensive Action of Parathyroid Hormone-(1–34) Fragments in Hypertensive Rats (41253)

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Abstract. The acute hypotensive action of bovine and human parathyroid hormone-(1–34) fragments given intraarterially to normotensive and hypertensive rats was examined. Spontaneously hypertensive, two-kidney, one-clip hypertensive, and deoxycorticosterone and salt hypertensive rats were used. Mean blood pressure was recorded without anesthesia or restraint through a cannula inserted into the abdominal aorta. Bovine and human parathyroid hormone-(1–34) fragments reduced blood pressure dose dependently in hypertensive rats as well as in normotensive controls. The degree of blood pressure decrease was greatest in deoxycorticosterone and salt hypertensive rats.

Handler *et al.* reported first in 1951 that parathyroid extracts increase renal plasma flow and decrease blood pressure in dogs (1). The parathyroid extracts used were very crude, and the vasodilatory effect of parathyroid hormone (PTH) has been largely ignored. Charbon *et al.* showed that a synthetic bovine PTH-(1–34) fragment has a hypotensive effect similar to that of parathyroid extracts in dogs (2, 3). Recently, Pang *et al.* also demonstrated the hypotensive effect of bovine PTH-(1–34) fragment given intravenously to several vertebrates (4, 5). They suggested that this action of PTH was due to a direct vasodilatory action (6, 7).

In an abstract, Pang and Yang reported the hypotensive effect of a bovine PTH-(1–34) fragment in spontaneously hypertensive (SHR) rats (8). Thus we determined hypotensive effects of bovine and human PTH-(1–34) fragments in normotensive and hypertensive rats. We compared three models: SHR; two-kidney, one-clip (CLIP); and deoxycorticosterone and salt (DOC) hypertensive rats, assuming that PTH might have some pathophysiological roles if the fragments showed stronger hypotensive action in either type of hypertensive rats. Blood pressure was determined through a cannula inserted into the abdominal aorta without anesthesia or restraint. The results indicated that both bovine and human PTH-(1–34) fragments were hypotensive in normotensive and hypertensive rats. A preliminary report of this work was presented at the XVIth Annual Meeting of Council for SHR, Yamagata, Japan, October 1980 (9).

Materials and Methods. *Hypertensive rats.* Male SHR of F37 from the colony of the Department of Pharmacology, Jichi Medical School, 15 weeks of age, were used. CLIP hypertension was induced by constricting the left renal artery with silver ribbon (slit width 0.2 mm) and leaving the contralateral kidney intact in 6- to 7-week-old male rats of HOS: Donryu strain (DON). Only the rats whose blood pressure exceeded 150 mm Hg as measured by a tail manometer (Natume Seisakusho, KN-0090) were used 6–7 weeks after surgery. DOC hypertension was made in 6- to 7-week-old male DON rats by left nephrectomy, giving a 1% NaCl solution to drink, and treating with deoxycorticosterone acetate, 8 mg/kg/week, sc. The experiments started 6–7 weeks after DOC treatment had begun. Twelve-week-old DON rats served as the normotensive control. Each normotensive and hypertensive group consisted of 9 or 10 rats.

Determination of blood pressure and experimental protocols. A polyethylene cannula was inserted into the abdominal aorta of rats under ether anesthesia. Mean blood pressure was recorded after 48–72 hr through the cannula without anesthesia or restraint by an electronic system (YHP 1280C, YHP 8850A, and Yokogawa Electronic 3046C) (10). PTH fragments, 1, 3, and 10 μg/kg, were injected intraarterially

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through the cannula inserted into the abdominal aorta. An injection of physiological saline solution (1 ml/kg) did not appreciably affect blood pressure. Each injection was followed by injecting 0.2 ml of physiological saline to flush the cannula. The change in mean blood pressure was determined as the difference between the value before injection and the lowest value after injection. We waited at least 20 min after a single injection to recover mean blood pressure to the preinjection level.

Each bolus injection of three doses of a fragment was given to a rat. The same rat was used for the study of another fragment on the following day. Bovine fragment was given first to half of the rats and human fragment was applied first to the remaining rats.

PTH fragments. Bovine and human PTH-(1−34) fragments were purchased from Peninsula Laboratories (San Carlos, Calif.) and Protein Research Foundation (Minoh, Osaka-fu, Japan), respectively. The fragments were dissolved in physiological saline in a volume of 1 ml/kg.

Statistical analyses. The data are expressed as mean ± SEM. Statistical analyses were made by using Scheffé's *S* test.

Results. Blood pressures determined at the tail were 161 ± 4, 183 ± 8, and 205 ± 8 mm Hg in SHR, CLIP and DOC rats, respectively. CLIP hypertensive rats whose blood pressure exceeded 150 mm Hg were used. Figure 1 shows typical records of mean blood pressure in normotensive and DOC hypertensive rats treated with human PTH-(1−34) fragment. This fragment decreased blood pressure dose dependently. Blood pressure reached a plateau within 2−3 min, and lasted for 2−30 min.

Hypotensive effects of bovine PTH-(1−34) fragment in normotensive and three types of hypertensive rats are shown in Fig. 2. The fragment also decreased blood pressure dose dependently. The effects were almost the same in SHR and normotensive rats, and slightly greater in CLIP and moderately in DOC rats. When the effects were expressed as a percentage of the initial values, the same tendencies were seen except in SHR rats, whose responses became slightly weaker than those of the control rats.

Hypotensive effects of human PTH-(1−34) fragment in normotensive and hypertensive rats are shown in Fig. 3. The effects were slightly weaker in SHR, slightly greater in CLIP, and moderately greater in DOC rats than in normotensive control rats. When the effects were expressed as a percentage of the initial blood pressure, the same tendencies were seen except in CLIP rats, whose responses became equal to those of the control rats.

Discussion. In the present study we

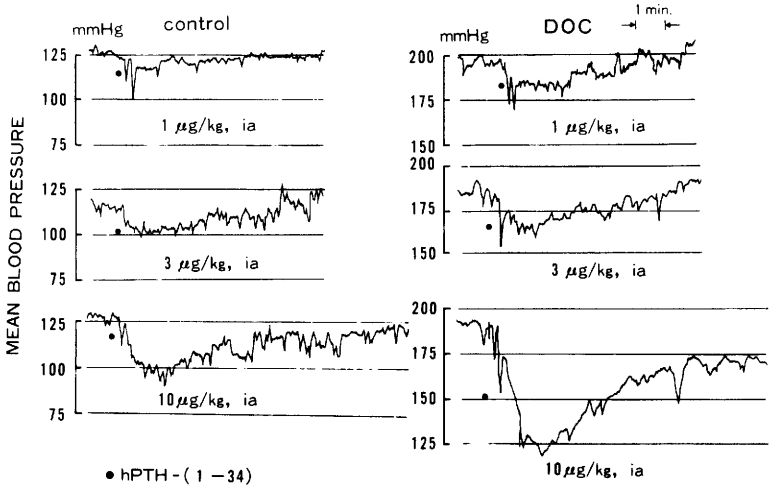

FIG. 1. Typical mean blood pressure changes in normotensive control and deoxycorticosterone and salt (DOC) hypertensive rats treated with human(h) PTH-(1−34) fragment. Abscissa is time. (●) Site of fragment injection.

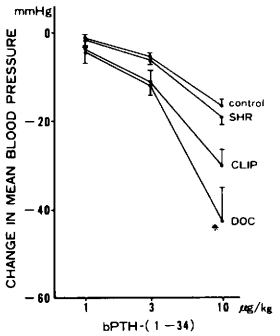

FIG. 2. The hypotensive effects of bovine(b) PTH-(1–34) fragments in normotensive and hypertensive rats. SHR: spontaneously hypertensive rats. CLIP: one-clip, two-kidney hypertension. DOC: deoxycorticosterone and salt hypertension. Data are shown mean ± SEM. $*P < 0.05$ compared to normotensive control.

showed acute hypotensive actions of bovine and human PTH-(1–34) fragments in normotensive and hypertensive rats. SHR, CLIP, and DOC hypertension were used. Among them, DOC hypertension was the most sensitive to the fragments. The present studies confirmed the previous report by Pang and Yang (8) on the hypotensive action of bovine PTH-(1–34) fragment in SHR rats. Hypotensive effect of human PTH-(1–34) fragment in normotensive DOC rats was also shown first in the present study.

At present we could not answer the question why DOC hypertension was more sensitive to the fragments, whereas SHR rats were relatively less sensitive than CLIP ones. However, it is possible that

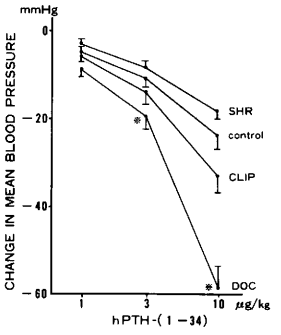

FIG. 3. The hypotensive effects of human(h) PTH-(1–34) fragments in normotensive and hypertensive rats. Abbreviations are the same as in Fig. 2.

PTH might be involved more intensively in the pathogenesis of DOC hypertension than those of the other types of hypertension. Further studies are necessary to elucidate this.

It is well known that the (1–34) fragment is essential for PTH action. The bPTH preparation and bPTH-(1–34) fragment have about equal hypotensive potencies (4). Pang *et al.* (5) recently reported hypotensive action of bPTH-(24–28) and ineffectiveness of bPTH-(25–27), suggesting that five amino acids in positions 24–28 are responsible for hypotensive action of PTH fragments. Plasma concentration of PTH is less than 1 ng/ml (11). It corresponds to about 0.4 ng/ml of the (1–34) fragment. When 1 μg/kg of the PTH fragment is injected into the rat, plasma concentration may reach 20–30 ng/ml. From this calculation, we could speculate that the hypotensive action of PTH-(1–34) fragments is pharmacological rather than physiological.

Besides the role of PTH in normal blood pressure regulation, we know little of its role in hypertensive states. Parathyroid function is known to be enhanced in essential hypertension (12). Plasma PTH levels are higher in SHR and DOC hypertensive rats (13, 14). The incidence of hypertension is high in hyperparathyroid patients (15). Furthermore, parathyroidectomy deteriorates the developmental course of hypertension in DOCA–salt-treated rats (16). All of the above evidence indicates a hypertensive nature of PTH. If so, the observed hypotensive action of PTH fragments may be physiologically significant, because the action could antagonize the hypertensive nature of PTH when it is released to increase plasma calcium concentration.

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