Effect of Somatostatin on Plasma Renin Activity and Blood Pressure in Patients with Essential Hypertension

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Abstract

The effects of somatostatin on plasma renin activity (PRA) and blood pressure were evaluated in patients with essential hypertension (EH) and in normotensive subjects. All subjects examined were hospitalized and placed on a diet containing 7-8 g/day sodium chloride and received an intravenous infusion of somatostatin (500 µg/20 ml of saline, for 60 min) in the basal condition. During somatostatin infusion, the mean blood pressure (MBP) remained unaffected in all patients with EH and the normotensive subjects, while the PRA decreased slightly in the EH group. When the patients with EH were classified according to their renin levels (low, normal and high), parallel significant decreases in MBP and PRA were found only in the high renin group during the somatostatin infusion. No significant change in MBP and PRA was observed in the other groups including the normotensive subjects.

To assess the activity of synthetic somatostatin, the plasma levels of growth hormone (GH) and cyclic AMP were measured. These levels were lowered significantly during the infusion and the GH levels showed a rebound 15 min after cessation of the infusion. The cyclic AMP returned to the basal levels, but no rebound was observed.

The above data indicate that the fall in blood pressure in the high renin group in the basal condition was probably due in part to reduced renin release by somatostatin, and the maintenance of high blood pressure especially in high renin EH.

Earlier reports have demonstrated that exogenous somatostatin suppressed the enhanced plasma renin activity (PRA) induced by furosemide stimulation (Rosenthal et al., 1976, Gomez-Pan et al., 1976), beta-adrenergic stimulation (Rosenthal et al., 1977) and pentobarbital anesthesia (Izumi et al., 1979) and decreased the PRA in the basal condition in high renin essential hypertension (EH) (Rosenthal et al., 1978). The PRA inhibiting mechanism of this peptide was considered to be similar to that of a beta-receptor-blocking agent. Rosenthal et al. (1977) reported that increased PRA and blood pressure induced by orciprenalin was suppressed by somatostatin administration. As described by Naftilan et al. (1978), it is well known that beta-stimulator induces renin release in vitro. We previously reported that renin release in dog renal cortical cell suspensions during incubation for 1 hour at 37°C was inhibited by somatostatin (Izumi et al., 1979). It is thought therefore that the increase in renin release in vitro caused by beta-adrenergic stimulation may be suppressed by this peptide.

At the cell level, somatostatin may act by impairing cyclic AMP production in the anterior pituitary gland or pancreas (Borgeat et al., 1974; Efendic et al., 1975).

Received March 15, 1980.
Michelakis et al. (1969) demonstrated cyclic AMP-enhanced renin release in vitro. The mechanism of the inhibitory effect of somatostatin on renin release may thus involve suppression of cyclic AMP generation.

The present report describes the effects of somatostatin infusion on PRA and blood pressure in patients with EH and in normotensive subjects. The plasma levels of growth hormone (GH) and cyclic AMP were also determined to assess the activity of the peptide used in this study.

**Experimental Subjects and Methods**

The subjects examined were 15 male patients with EH, aged 19 to 51 years (34.8±3.3, mean±SE) and 6 male normotensive subjects, aged 29 to 34 years (30.4±0.9) and their informed consent was obtained. The diagnosis of EH was established by excluding known causes of secondary hypertension. Clinical and laboratory findings for the patients are summarized in Table 1. The classification of hypertensive subjects into low, normal and high renin groups was made by the criteria of Honda et al. (1978), giving 5 patients with low renin, 6 with normal renin and 4 with high renin. Each normotensive subject was confirmed to lack evidence of any metabolic, endocrine or cardiovascular disorder. In all subjects, antihypertensive medication or medical care was stopped at least 2 weeks before admission and a constant dietary regimen containing 7-8 g NaCl/day was maintained.

The study was begun between 8 and 9 a.m. after overnight recumbency. The left great saphenous vein and left antecubital vein were cannulated for infusion and blood sampling, respectively. Blood pressure was measured in the right arm.

Prior to somatostatin infusion, blood sampling and blood pressure measurement were carried out twice (at 5 min intervals) to obtain baseline values. The peptide (500 μg/20 ml of saline) was then infused with a constant infusion pump over 60 min. Blood samples were obtained at 15 min intervals during infusion, and 15 and 60 min after cessation of the infusion. Blood pressure was measured at the same time points. Samples for GH determination were obtained from 14 patients, for cyclic AMP from 7 of the patients, and for PRA from all individuals including the normotensive subjects. Unfortunately, the determination of the plasma level of cyclic AMP became possible only in the latter half of the present study and was carried out in only 6 patients with normal renin EH and 1 patient with high renin EH.

The radioimmunoassay procedure for PRA followed the method of Haber et al. (1969). GH was determined by the original method of Schalch and Parker (1964), and cyclic AMP by a modification of the method of Steiner et al. (1973).

Synthetic somatostatin was obtained from Serono Pharmaceuticals, Freiburg.

The results were expressed as mean±standard error (SE). Statistical analysis was performed by the Student’s paired t test, and P values of less than 0.05 were considered statistically significant.

**Results**

As shown in Fig. 1 (upper graph), the somatostatin infusion elicited subjective evidence of GH inhibition since plasma GH decreased as much as 35%-59% throughout the infusion period (to 1.5±0.5-0.9±0.1 ng/ml, mean±SE) from a basal level of 2.2±0.6 at 0 min. After discontinuation of the infusion, the GH showed a rebounded to a level of 2.9±0.5 within 15 min and then returned to a level close to the basal value within 60 min (2.0±0.3).

The lower graph in Fig. 1 shows the changes in plasma cyclic AMP induced by the somatostatin administration. Cyclic AMP dropped from a basal level of 27.4±2.3 pmol/ml at 0 min, by 26%-30% to 20.2±1.2-19.3±0.8 pmol/ml (mean±SE) during the infusion, and returned to a level
Fig. 1. Effects of somatostatin on plasma levels of of growth hormone (GH) (n=14) and cyclic AMP (n=7) in patients with essential hypertension. Closed circles and vertical bars represent mean±SE. The P values (*P <0.05, **P<0.01) express statistically significant changes from pretreatment values.

(27.2±2.2) close to the basal value 15 min after discontinuation of the infusion.

Figure 2 summarizes the effects of the somatostatin infusion on MBP (upper graph) and PRA (lower graph) in all patients with EH. The MBP during somatostatin infusion remained essentially unchanged, while a small but statistically significant decrease in PRA was observed 30 and 60 min after initiation of the infusion. The basal level of PRA at 0 min was 5.3±0.9 ng/ml/h (mean±SE) and fell to 3.3±0.5, 3.4±0.5 and 3.4±0.6, in 30, 45 and 60 min, respectively, after the beginning of somatostatin infusion. Recovery of the PRA level was initiated within 15 min after the end of infusion.

Discussion

Following its isolation from ovine hypothalamus as a growth hormone release inhibiting hormone somatostatin has been recognized as a factor inhibiting for various hormonal secretions. Recently, investigations with exogenous somatostatin have been extended to the cardiovascular system, and the peptide has been characterized as a suppressor of PRA, blood pressure, and the cardiac and stroke index (Rosenthal et al., 1978). The present study was performed essentially to confirm and extend previous results. However, preliminary work revealed that infusion of 500 µg of somatostatin over 1 hour resulted in a decrease in PRA, together with a decrease in blood pressure in 2 patients with renovascular hypertension in the basal condition. The investigation was therefore planned expecting such decreases, not only in PRA but also in blood
pressure in patients with high renin EH in the basal condition. The observed somatostatin-induced parallel decreases in PRA and MBP in the high renin group in the basal condition were not consistent with the results of Rosenthal et al., (1978), since only the PRA level was decreased in their study under the same experimental conditions. Differences between the somatostatin administration methods used in the two studies may account partially for these conflicting results. In their study, 250 μg of somatostatin was injected first as a priming does in a bolus and then, another 250 μg/h was infused continuously for 2 hours. The overall dose rate of 375 μg/h was thus smaller than our 500 μg/h for 1 hour. When we administered somatostatin by the same method as Rosenthal et al., the intravenous bolus injection of the peptide dissolved in 10 ml of saline caused tachycardia, high blood pressure and a feeling oppression of the chest. The mechanism whereby a high concentration of the circulating peptide following acute administration induced untoward clinical symptoms remains unexplained. The suppressing effect of somatostatin on PRA is probably not dose-dependent, since we have previously shown that intrarenal arterial infusion of the peptide was increasingly effective in lowering the PRA in the renal vein when the administered dose was decreasing (Izumi et al., 1979). Secondly, to classify EH patients according to their renin levels, we followed the criteria of Honda et al., in which the division was based on both the basal and furosemide-stimulated condition. The detailed criteria undoubtedly differ from those used by Rosenthal et al. Thirdly, the genesis of EH is considered to show some disparity between Japan and Europe.
In spite of a capacity for larger percent decreases in PRA following somatostatin administration than in our study, they did not observe decreases in MBP. These findings raise the question of whether the hypotensive effect of the peptide might result not only from a fall in renin release. Other mechanisms might, for example, exert an influence on the cardiac and stroke index, as indicated by Rosenthal et al. (1978). Anyway, the effect of somatostatin on blood pressure in this study is quite similar to the propranolol-induced antihypertensive action in the previous study (Bühler et al., 1973). It is therefore strongly suggested that the hypotensive action of somatostatin is related directly, in part, to a reduction in renin release.

Concerning the mechanism of inhibition of PRA by somatostatin, we have reported evidence of a direct action on renin producing cells after preparing dog renal cor-
tical cell suspensions (Izumi et al., 1979). Rosenthal et al. assumed that somatostatin could be characterized as a beta-blocker and action as an alpha-blocker was discounted by Schmitt et al. (1979). It was reported by Niftilan et al. (1978) that renin release in vitro was enhanced by a beta-stimulator. A relationship between renin release and cyclic AMP had been previously proposed (Hamet et al. 1974). On the basis of these views, it can be inferred that parallel decreases in renin release and cyclic AMP due to somatostatin action could occur in in vitro experiments.

Determination of the plasma levels of GH and cyclic AMP were carried out to assess the efficiency of exogenous somatostatin in vivo. The GH levels were suppressed, as observed in many previous studies (Brazeau et al., 1973; Mortimer et al., 1974; Brzeau et al., 1974). The inhibition of plasma cyclic AMP levels in the present study is probably in agreement with the previous report of Herthelendy et al. (1977) in which urinary cyclic AMP excretion in the rat was inhibited by somatostatin administration. Although some evidence supports a relationship between control of renin release and cyclic AMP (Hamet et al. 1974), the significant decrease in plasma level of cyclic AMP observed in the present study could not verify this relationship between renin release and cyclic AMP. Rasmussen (1970) stated in his review that cyclic AMP has been implicated as an intermediate in the action mechanism of many hormones at the cell level. The observed reduction in this nucleotide in the present study might have resulted from the effects of somatostatin on several organs in vivo. In any case, the reduction of GH and cyclic AMP clearly demonstrated the activity of exogenous somatostatin in our study.

In conclusion, it can be said that the present results indicate that only patients with high renin EH were strongly affected by exogenous somatostatin to give parallel decreases in PRA and blood pressure. Also the exogenous somatostatin in the present study modified the PRA and blood pressure through pharmacological action. Further detailed studies on the physiological role of this peptide as a renin inhibitor are required.

References
