Increased Renin Release Evoked by Mesencephalic Stimulation in the Dog

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Effects of electrical stimulation of mesencephalic pressor areas (central gray stratum and adjacent portions) on renin secretion were studied in the dogs anesthetized with z-chloralose. The stimulation areas of the brain were determined using stereotaxic method. Renin release was estimated by taking renal vein and femoral artery blood samples simultaneously. Plasma renin activity was measured by assay in the rats of angiotensin produced by incubation.

Renin release increased markedly during the stimulation and this increase was eliminated by renal denervation. The electrode positions most effective in causing increased renin release were distributed in dorsal portion of mesencephalic pressor areas, which gives selective effect on renal vascular beds according to our previous study.

These results suggest that central nervous system plays some role in the regulation of renin secretion.

There has been a growing body of evidences that renal pressor system and sympathetic nervous system relate each other. Indeed many investigators have recently elucidated the role of renal nerve and catecholamines in renin secretion. But the responses of renin secretion to the central nervous system activity have not yet been reported, though it seems to play the most important role in the relationships between renal pressor system and nervous system.

We have been working on vasomotor effects of midbrain stimulation and have clarified that this area gives the most prominent sympathetic response constantly. Furthermore, dorsal portion in this area has proved to exert selective influence on renal vascular beds.

This report is an attempt to determine, as the first step of our investigations, whether central nervous system stimulation gives any influence on renin secretion or not. We have chosen midbrain for the first trial of stimulation, because it is most likely place to give positive effect on juxtaglomerular apparatus, if any.

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MATERIALS AND METHODS

Twenty-two adult mongrel dogs of both sexes weighing between 8 and 12 Kg. were anesthetized with 80 to 100 mg./Kg. of α-chloralose administered intravenously. The animals were fixed in a stereotaxic instrument and the skull was exposed and opened over selected stimulation areas. A concentric bipolar needle electrode insulated except for tip was inserted stereotaxically into mesencephalic pressor areas. A stimulator with isolating unit was used to deliver square-wave pulse of 100 cps in frequency, 5 v. in amplitude and 1 msec. in duration. Period of stimulation was 4 min. After each experiment an electrolytic lesion was produced by passing direct current. The precise position of electrode tip was identified in the brain fixed in formalin saline and potassium ferrocyanide.

To obtain venous blood samples a catheter was introduced into jugular vein, passed down vena cava and led into renal vein under fluoroscopy. Arterial blood samples were obtained by femoral catheter. Blood pressure was monitored by an electric manometer connected to femoral artery of another side. Arterial and venous blood samples were obtained simultaneously before, during and after the stimulation.

In 4 animals effect of renal denervation was examined. Left renal pedicle was exposed retroperitoneally and dissected all hilar tissues except for renal vessels and ureter. Renal vessels were stripped of visible nerve fibers and painted with lidocaine. Catheters were introduced into both sides of renal veins through jugular and femoral veins under fluoroscopy and venous blood samples were taken simultaneously from both sides.

Assay of renin activity: Five ml. of blood samples were collected with EDTA in polyethylene tubes in an ice bath and were centrifuged at 0°C. The plasma was removed and stored frozen. Then the plasma was added with 1 drop of 0.1% DFP, adjusted to pH 5.5 and incubated for an hour at 37°C. The plasma was boiled for 10 min. and centrifuged. Angiotensin produced in supernatant was bioassayed for pressor activity, compared with standard angiotensin II (Ciba Hypertensin), in vagotomized rats given pentobarbital, pentolinium and phenoxybenzamine.

In 5 dogs response of renal blood flow to the midbrain stimulation was observed using an electromagnetic flowmeter with its probe place in the circuit between common carotid and renal artery.

RESULTS

(1) Response of blood pressure

By the stimulation blood pressure rose immediately about 100% of previous level with tachycardia, reached the peak in about 20 sec., then maintained the peak level with bradycardia and then gradually fell. By cessation of the stimulation blood pressure returned to the control level.

(2) Response of renal blood flow (Fig. 1)

Changes of renal blood flow were reduction consisting of 2 stages.
first stage was transient and was converted to the increase by renal denervation. In the second stage renal blood flow decreased to the half or less of the control level in its initial portion and then began to increase in spite of continuing the stimulation. This stage was abolished by injection of dibenamine after denervation. Thus it was concluded that the first stage was caused exclusively by nervous activity and the second stage by the combination of nervous activity and catecholamines released by the stimulation. In addition total decrease of renal blood flow by prolonged stimulation was small compared with changes of renin activity in renal vein blood.

(3) Response of renin release

Fig. 2 illustrates a typical experiment, in which renin activity in renal
Fig. 2. An example of effect of midbrain stimulation on renin release. From top down, systemic blood pressure, assay record of renin activity in renal vein blood and renin activity in arterial blood.

ven blood increased during and immediately after the stimulation, while that in arterial blood increased slightly only after the stimulation. As shown in Fig. 3, renal V-A difference of renin activity increased during the stimulation as much as 900% of the control level (mean value: 495%) in about half of the cases. Therefore the increased renin release could be suspected in such cases. Delayed elevation of arterial renin activity, which means increase of total circulating renin, is another evidence of increased renin release.

Effect of renal denervation is demonstrated in Figs. 4 and 5. Response of renin release was eliminated in the left side by the denervation, though not completely, while it was marked in the intact right side.

As shown in Fig. 6 increased renin release seems to accompany a higher elevation of systolic and diastolic pressure and a longer duration of pressor response, although relations are not significant.

(4) Sites of stimulation in the midbrain

Electrode tip positions inducing typical pressor response were distributed in central gray stratum and its adjacent portions. But stimulation points
Fig. 3. Changes in plasma renin activity by mesencephalic stimulation. Solid line indicates renal vein blood and dashed line arterial blood respectively.

Fig. 4. An example of renal denervation experiment. Upper tracing: systemic blood pressure. Middle tracing: assay record of renin activity in renal vein blood of innervated side. Lower tracing: denervated side. Numbers under each assay record refer to volume of plasma injected into rat.
Fig. 5. Effect of renal denervation on the response to mesencephalic stimulation. Left panel: Changes of renin activity in renal vein blood of innervated side. Right panel: denervated side.

giving positive result in renin release were clearly localized in dorsal portion in this pressor area on histological examinations as shown in Fig. 7.

DISCUSSION

Vander, Wathen et al. and Page et al. have elucidated that the electrical stimulation of renal nerve or intraarterial injection of catecholamines evokes renin release. In addition Hodge et al. and Ueda et al. demonstrated role of renal innervation in the hemodynamic stimulation of renin release. Thus it is obvious that increased nerve activity and catecholamines can give positive effect on renin release. But comprehension of relationships between nervous system and renal pressor system is incomplete without studying the role of central nervous system. Furthermore, Ueda et al. studied the effect of chronic stimulation of diencephalon on blood pressure in the rabbits with and without unilateral renal artery constriction. They have succeeded in producing prolonged elevation of blood pressure in animals with ischemic kidney. Thus it is considered that sympathetic nervous system and renal pressor mechanism may act synergetically to induce sustained elevation of
blood pressure. The present investigations were undertaken to clarify the relationships between central nervous system and renal pressor mechanism.

By the stimulation of midbrain renal V-A difference of renin activity increases markedly. In contrast, decrease of renal blood flow is slight when blood samples are taken, though it is prominent in initial portion. Therefore it is evident that increased V-A difference of renin activity indicates renin release from the kidney by mesencephalic stimulation. Delayed elevation of arterial renin activity is another evidence for the increased renin release. Our another data that midbrain stimulation evokes increased aldosterone secretion, may also support present conclusions.

But in about half the cases we had negative result, so we analysed the conditions concerning sites of stimulation and hemodynamic responses. Figs. 6 and 7 reveal that electrode tip position is most intimately related to the renin release. That is, dorsal portion in the pressor area is responsible for renin release. In our previous study\(^9\) we disclosed that this dorsal portion

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**Fig. 6.** Analysis of factors in hemodynamic response and electrode position determining renin release. White circles indicate increased renin release, black circles negative result respectively.
Fig. 7. Electrode tip position in the midbrain. Circles indicate position giving increased renin release. Triangles indicate position giving negative result.

gives selective and differentiated constrictor effect on renal vascular bed. Present result is compatible with this study in that stimulation exerts effects through nervous pathway on the kidney.

Experiment of renal denervation also confirms that the effect of midbrain stimulation is conveyed to the kidney mainly by renal nerves.

As effects of nervous activity and catecholamines on intrarenal hemodynamics and electrolytes in tubular fluid are not fully known, we can not as yet conclude whether nervous system exerts its effect directly on juxtaglomerular cells or indirectly through changes of hemodynamics or electrolyte metabolism. But our result suggest that central nervous system plays at least some role in the regulation of renin secretion.

Pressor areas in the midbrain are supposed to be sympathetic descending pathway or relay station between diencephalon and medulla oblongata and other lower structures.11) Rather scattered neurones in the diencephalon concentrate in the mesencephalon, therefore we can evoke maximal typical excitation of sympathetic nervous system most consistently and easily by stimulating this area. In addition we are aware that dorsal portion gives selective influence on renal vascular bed. However, whether this place has some specific value in renin secretion has not been clarified by the present investigation. We are now investigating the effects of stimulation of other areas in brainstem including hypothalamus and preoptic area.
Midbrain stimulation evokes behavior response much like "defence reaction" or "sham rage". Thus it is highly probable that renal pressor system takes part in such reactions.

SUMMARY

Effects of electrical stimulation of the mesencephalic pressor area (central gray stratum and adjacent portions) on renin release were studied in the chloralosed dogs.

Renin release was measured by simultaneous collection of arterial and venous blood samples taken by the catheter introduced into renal vein under fluoroscopy.

Mesencephalic stimulation provoked marked increase in renin release. Dorsal portion of mesencephalic pressor area is more effective than ventral portion in inducing renin release.

REFERENCES