Experimental Studies on the Nervous Control of the Renal Circulation—Effect of the Electrical Stimulation of the Medulla Oblongata on the Renal Circulation

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An attempt was made to analyse the medulla oblongata in relation to the effect of electrical stimulation on the renal circulation in 40 anesthetized dogs. The stimulation evoked various responses in arterial pressure and in renal blood flow. To avoid possible influences of humoral factors and of prerenal circulatory changes an innervated kidney was perfused in situ by the donor's blood in 20 dogs. Stimulation of the lateral reticular formation evoked a rise in blood pressure with a concomitant decrease in renal blood flow. This decrease in renal blood flow was ascribed to renal vasoconstriction. Stimulation in the dorsal part of the reticular formation occasionally produced an increase in renal blood flow during a pressor response. Since the renal vascular resistance showed little or no significant change in the perfused kidney on stimulation in this area, the observed increase in renal blood flow seemed to be passive one. On stimulation in the medial reticular formation, the depressor area, renal blood flow was ordinarily decreased with unaffected renal vascular resistance. In some dogs, stimulation in the reticular formation adjacent to the solitary tract caused a decrease in renal vascular resistance together with a pressor response, suggesting that central effects of vagal stimulation can be elicited by local stimulation of the bulb. However, stimulation of the dorsal vagal nuclei and of the nucleus ambiguus did not result in renal vasodilatation. Vagotomy did not modify an increase in renal blood flow caused by stimulation. Thus, there was no evidence of active renal vasodilatation.

THE nervous control of the renal circulation has been the subject of many studies, but the role of the central nervous system on this

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vascular circuit has not been fully analysed. Previous papers of this laboratory demonstrated that the blood pressure elevation induced by diencephalic stimulation was usually associated with an increase in renal vascular resistance. But, on stimulation in some parts of the diencephalon, no significant change in resistance in the renal vessels was caused during a fall in blood pressure.^{1), 4)} On the other hand, stimulation of the central end of the vagal or some somatic nerves evoked a variety of responses in blood pressure and in renal vascular resistance. In some dogs, even renal vasodilatation accompanied by a pressor response was observed.^{2), 3)} Thus, these mixed findings suggested that response of the renal vascular bed to electrical stimulation of the central nervous system depended upon the stimulated structure and that, furthermore, the response might occasionally differ from that of the body. Since afferent stimulation of the vagal or various somatic nerves is considered to elicit cardiovascular reflexes, at least in part, via the medulla oblongata,⁵⁾ a systematic study of the influence of medullary stimulation on the renal circulation might give an answer to this question. Studies in such aspects, however, have been few in number. The following experiments were designed to investigate this presumption by measuring renal blood flow directly with an electromagnetic flow meter.

METHODS

Forty adult mongrel dogs, of both sexes, weighing 8.8 to 15.8 Kg., were used in the experiments. They were anesthetized with morphine chloride (3 mg./Kg.) plus chloralose (80 mg./Kg.). The systemic arterial pressure was recorded by means of an electromanometer connected to the cannulated femoral artery and the renal blood flow was simultaneously recorded by an electromagnetic flow meter which was inserted in circuit between renal vein and femoral vein. Usually the left kidney was used and the spermatic or ovarian vein was tied separately. The connections were made by polyethylene tubes as closely as possible and care was taken to minimize the damage to the renal nerves. Heparin was given intravenously to prevent clotting, generally in doses of about 25 mg. per Kg. body weight.

In 20 experiments, an innervated kidney was perfused in situ by the donor's blood to avoid possible influences of humoral factors and of prerenal circulatory changes. The technique employed has been described in a previous paper.³⁾ In these cases, the perfusion pressure of the recipient's kidney being kept constant, changes in resistance in the renal vessels were expressed as reciprocals of changes in renal blood flow. Bilateral cervical vagotomy and sinus nerve cutting were usually carried out in the course of each experiment. In some instances, artificial respiration was given to maintain even ventilation. The lower brain stem was exposed by removing a part of the occipital bone and retracting the cerebellum. The stimulation was applied with fine bipolar electrodes by means

of a stereotaxic apparatus. The electrodes consisted of two dental broaches, made of piano wire, 0.13 mm. in diameter and 52 mm. long. These broaches were cemented and insulated except for the tips.

The electrical stimuli used were rectangular voltage pulses having a duration of 1 msec. Stimulation frequency varied from 30 to 100 cps, but was maintained at 100 cps in most cases. Intensities varied from 1.0 to 15.0 volts, mostly being in the range of 1-5 volts. The duration of stimulation was 10 or 20 sec. After the experiments, the brains were examined histologically for localizing the stimulated points. The maps described correspond to plates c-9, 11, 13, and 15 of the atlas of Lim et al.⁶⁾

RESULTS

Experiment 1

On total of 94 points in the caudal portion of the medulla oblongata, 398 electrical stimulations were carried out in 20 dogs. Stimulated sites in the medulla oblongata were chosen which were assumed to participate primarily in cardiovascular control. Therefore, the reticular formation and the vagal nuclei of origin and termination were chiefly concerned in the experiments. Various response patterns in blood pressure and in renal blood flow were obtained, depending on the stimulated sites. The results are presented in Table I and the typical patterns are demonstrated in Fig. 1. In Fig. 2A, the stimulated points are mapped out.

Table I. Results of Changes in Blood Pressure and in Renal Blood Flow Observed in Exp. 1

BP RBF	Pressor response	No change	Depressor response	Total
Decrease	128	6	43	177
No change	18	160	11	189
Increase	27	3	2	32
Total	173	169	56	398

Changes in blood pressure: As seen in Fig. 2A, marked pressor responses were generally obtained from stimulation of the lateral and dorsal reticular formations at these levels of the bulb. Depressor responses, on the other hand, were evoked from the medial reticular formation. When the vagi were intact, stimulation of the dorsal vagal nuclei and of the adjacent area produced depressor responses with marked bradycardia. But, infrequently, pressor responses were also elicited despite of slow heart rate from stimulation in the adjacent area of the dorsal vagal nuclei. Diphasic responses were observed with cessation of stimulation in the

Fig. 1. Various patterns of responses in blood pressure and in renal blood flow, observed in Exp. 1. Stimulation of the medulla oblongata with 100 cps, 1 msec., at 1-8 volts for 10 sec. (A-H) and 20 sec. (I).

majority of the experiments, but those during stimulation were noted only in 7 instances. In 10 experiments, a depressor response reversed to pressor one by shifts in stimulation voltage in the depressor area. The relationship between percent change in blood pressure and stimulation voltage in these cases is seen in Fig. 3. Maximal depressor responses were obtained already at 3~5 volts and, beyond these limits, the stimuli tended to elicit pressor responses. Because of these findings, only 5 volts was used as the most suitable parameter for mapping in the experiments.

Patterns of response: Stimulation of the pressor area generally produced a rise in blood pressure and a decrease in renal blood flow (Fig.

Fig. 2. Four serial cross sections of the lower brain stem at 2 mm. apart. Blood pressure responses are represented on the left side, and changes in renal blood flow on the right side. The vagi and sinus nerves were all intact. Stimulation parameters; 100 cps, 1 msec., 5 v., and 10 sec. A: Results of Exp. 1. B: Results of Exp. 2 (cross-perfusion experiments).

Abbreviations for all figures: acc cun Nucleus cuneatus accessorius; dvg Nucleus dorsalis n. vagi; h Nucleus n. hypoglossi; lr Nucleus reticularis lateralis; inf ol Nucleus olivaris inferior; amb Nucleus ambiguus.

1,A). In the dorsal part of the reticular formation, however, stimulation occasionally elicited an increase in renal blood flow during a pressor response (Fig. 1,C). In these cases, the blood pressure elevation was usually accompanied by the widening of pulse pressure. At times, marked pressor responses were observed without changes in renal blood flow on stimulation in the pressor area, suggesting that a concomitant constriction of the renal vessels took place as at the same time the blood pressure elevated (Fig. 1,B). In some dogs, no significant change of blood pressure was recorded despite of a decrease in renal blood flow (Fig. 1,D), but vagotomy sometimes changed the response to that associated with a rise in blood pressure.

In the depressor area, stimulation evoked a fall in blood pressure

Fig. 3. The relationship between stimulation voltage and percent change in blood pressure. Stimulation of the depressor area. The other parameters were remained unchanged; 100 cps, 1 msec, for 10 sec.

together with a decrease in renal blood flow (Fig. 1,G). Exceptionally, with a depressor response, renal blood flow was increased in 2 experiments (Fig. 1,I). The degree of increase, however, was slight. On stimulation in the area adjacent to the dorsal vagal nuclei, a marked bradycardia with a depressor reaction was ordinarily evoked when the vagi were intact. Therefore, renal blood flow was exceedingly decreased. As for the nucleus ambiguus, stimulation of this nucleus or the adjacent area caused a rise in blood pressure accompanied by a decrease in renal blood flow. The insignificant response pattern in blood pressure and in renal blood flow was usually recorded with 1~3 volt stimulations (Fig. 1,E). Other response patterns were uncommonly observed in the course of the experiments (Fig. 1,F,H).

Experiment 2

The following experiments were performed to ascertain the possible changes in renal vascular resistance on stimulation of the medulla oblongata by perfusing one of the recipient's kidney with the donor's blood.

Stimulation was carried out at 90 points of the lower brain stem during this series of experiments. As seen in Table II, there were also

Table II. Results of Changes in Blood Pressure and in Renal Blood Flow Observed in Exp. 1

RBF \ BP	Pressor response	No change	Depressor response	Total
Decrease	105	6	26	137
No change	29	75	48	152
Increase	12	2	8	22
Total	146	83	82	311

various response patterns in blood pressure and in renal blood flow. In Fig. 2,B, the stimulated points are mapped out.

Stimulation in the pressor area usually produced the vasoconstrictor responses in the perfused kidney. In 6 experiments, only an increase of renal vascular resistance was observed without a significant elevation of blood pressure. However, in these occasions, vagotomy frequently made pressor response apparent. Contrary to this pattern, stimulation in the dorsal reticular formation not infrequently caused an insignificant change in renal vascular resistance with a pressor response. This pattern was usually found to be associated with the widened pulse pressure.

On stimulation in the depressor area, the renal vascular resistance was nearly unaffected in the majority of cases. In 6 points, renal vasoconstriction was evoked during a depressor response. A pattern of a

Fig. 4. The influences of shifts in stimulation voltage on changes in blood pressure and in renal blood flow. P.P. perfusion pressure of the kidney; B.P. arterial blood pressure of the recipient dog; RBF renal blood flow.

decrease in blood pressure associated with a decrease in renal vascular resistance was obtained in only 4 points.

When the vagi were remained intact, stimulation in the dorsal vagal nuclei elicited a marked bradycardia with a fall in blood pressure. In these cases, however, there was no observable change in renal vascular resistance.

Of interest is a pattern of an increase in blood pressure with a concomitant decrease in renal vascular resistance. This response pattern was frequently observed on stimulation in the reticular formation adjacent to the solitary tract. The characteristic feature of this response seemed to be accompanied by tachycardia with inspiratory activation of breathing. When the reactive point of this pattern was located, attempts were made to analyse in more detail the characteristics of the events. Fig. 4 shows a typical result. There was reversal of the direction of renal vascular resistance with alteration of stimulation voltage. Despite the magnitude of the blood pressure elevation depends on the stimulation voltage, the maximum decrease of renal vascular resistance is seen at 8 volts. In 9 points, in which this response pattern was observed, the relationship

Fig. 5. Changes in renal vascular resistance compared with concomitant changes in blood pressure on stimulation in the reticular formation adjacent to the solitary tract.

between changes in renal vascular resistance and in blood pressure was determined. Fig. 5 presents the result. The highest percentage decrease in renal vascular resistance does not exceed the limit of -40% and the decrease is usually converted to an increase in renal vascular resistance beyond the limit of $+30$ to $+40\%$ change in blood pressure.

However, responses of this pattern were nerve eliminated by bilateral vagotomy or with atropine in doses of 0.5 mg. per Kg. body weight.

DISCUSSION

Up to this time, several workers have contributed to the medullary control of the renal circulation. In 1936, Chen et al. showed on dogs that electrical stimulation in the pressor area of the medulla oblongata produced a rise in blood pressure with bilateral constriction of the kidneys.⁷⁾ Cort demonstrated that Trueta's renal shunt could be activated in cats by stimulating the vasomotor center in the medulla oblongata.⁸⁾ Recently, Wise and Ganong measured glomerular filtration rate by clearance method, stimulating various structures of the lower brain stem.⁹⁾ However, these investigations were generally carried out in comparatively restricted area and the localization of the stimulated points remained obscure.

The present studies demonstrated that medullary stimulation evoked various response patterns in blood pressure and in renal blood flow according to the stimulated sites in the bulb.

As for blood pressure responses, the localization of pressor and depressor areas confirmed the previous results described by Wang and Ranson and Alexander for the cat.^{10), 11)} The marked pressor responses were evoked chiefly from stimulation in the lateral reticular formation and the depressor responses without bradycardia were usually elicited from stimulation in the medial part of the reticular formation.

On the other hand, the alteration in renal blood flow was observed not always to vary in the same direction as the pressure responses. The results from Experiment 1 have shown that stimulation in a fairly wide area of the brain stem produces a decrease in renal blood flow. Stimulation in the lateral reticular formation caused a decrease in renal blood flow associated with a rise in blood pressure. Stimulation in the dorsal vagal nuclei and the medial reticular formation resulted in a marked decrease in renal blood flow with a fall in blood pressure. The increase in renal blood flow was elicited in occasional cases by stimulating in the dorsal reticular formation during a pressor response. Depressor reactions were rarely associated with an increase in renal blood flow on stimulation in the medial reticular formation.

Fig. 6. Possible influences of some secondary factors in the experiments. A: illustrates a response which implies a marked cardiac influence on renal blood flow. B: illustrates a pattern of an increase in blood pressure associated with a transient increase in renal blood flow during stimulation. C: illustrates a pressor response accompanied by a second wave with the long latent period, suggesting the participation of humoral factors.

From these findings, however, the primary neural effect on the control of renal circulation can hardly be assessed. Since the onset of these responses is usually in less than 4 sec. following stimulation, blood pressure changes seem to be elicited chiefly by neural mechanism. But, as for renal blood flow, it is difficult to rule out some possible secondary factors in the experiments. Hence, the alteration in renal blood flow can be explained in several ways: (1) When the vagi are intact, bradycardia is frequently observed. Therefore, the decrease in renal blood flow can not be ascribed to renal vasoconstriction immediately (Fig. 6A). (2) As seen in Fig. 6B, there sometimes occurs a transient increase in renal blood flow during stimulation. In these cases, it is possible that the increase in renal blood flow is secondary to a redistribution of blood from areas of increased vascular resistance. (3) Humoral factors also must be considered to be participated in the response in some occasions (Fig. 6C). Accordingly, it is desirable to eliminate some of these factors in order to analyse the neural control of the renal circulation more precisely.

In the second series of experiments, therefore, the renal blood flow was measured on the innervated kidney *in situ* perfused by another dog. In animals, so prepared that possible humoral factors and prerenal circulatory changes were excluded, any change in renal blood flow in response to electrical stimulation of the medulla oblongata can be ascribed to the direct neural effect on the renal vessels.

Thus, in Experiment 2, the kidney has been demonstrated to be concerned primarily in the vasomotor responses caused by stimulation in

the pressor area of the lower brain stem, with the exception of the dorsal reticular formation. It has been known that the reticular formation of the medulla oblongata consists of various nuclei as well as descending and ascending pathways. Therefore, the pressor area appears to have differentiated functions on the control of the renal circulation.

On stimulation in the lateral reticular formation, a rise in blood pressure was associated with a decrease in renal blood flow and the renal vascular resistance was increased in the perfused kidney, supporting the results of Chen et al. In the dorsal part of the reticular formation, stimulation frequently caused a pressor response accompanied by an increase in renal blood flow. However, cross-perfusion experiments revealed no or slight renal vasoconstriction. Consequently, this part of the reticular formation seems to hardly influence the renal vessels during a pressor response caused by stimulation. It would be also noteworthy that the evoked pressor response from the dorsal reticular formation was sometimes associated with the widening of pulse pressure, indicating active inotropic effect. Recently, several workers have postulated the regions whose stimulation exert excitatory influences on inotropic and chronotropic activities in the pressor area.¹²⁾⁻¹⁴⁾ Chai and Wang have reported that cardioaugmentor and cardioaccelerator centers exist in the dorsal reticular formation. Furthermore, according to Peiss, the augmented cardiac activity was sometimes observed without simultaneous vasoconstriction. To judge from these facts, the passive increase in renal blood flow, elicited from stimulation in the dorsal reticular formation in our experiments, would seem to be partly attributable to an increase in cardiac activities. Obviously, it can not be decided from the present experiments whether the other vascular circuits participated in this vasomotor response or not.

It is of interest that a pattern of a rise in blood pressure together with a decrease in renal vascular resistance was evoked by stimulation in the adjacent area to the solitary tract. With this pattern, not only cardiac acceleration but also facilitating influence on respiration, rapid shallow breathing, were repeatedly observed. Being not modified by vagotomy or with atropine, this renal vasodilatation seems to be due to inhibition of vasoconstrictor tone and there was no evidence of renal active vasodilatation. Since the solitary tract is known to mediate vagal afferent fibers, stimulation in this area may be assumed to be equivalent to central vagal stimulation. However, it should be noted that there is the discordance in the sympathetic control of the cardiovascular system. A possibility also exists that respiratory activity might be concerned in the responses. Weidinger et al. recently attempted to analyse the interaction between vasomotor and respiratory centers in the study of the localization of "bulbar sympathetic centers", recording synchronous

discharges from cardiac, renal, and phrenic nerves. But neither interplay between two centers nor disparity between efferent cardiac and renal impulses could be found.⁵⁾ On the other hand, Folkow et al. implied the possibility of differentiated activation of the functionally different autonomic neuron pools in the medullary vasomotor center through various excitatory means.¹⁶⁾ These possible aspects of the problem in this response pattern require further study.

In the medial reticular formation, stimulation ordinarily caused a decrease in renal blood flow associated with a fall in blood pressure, while cross-perfusion experiments revealed insignificant changes in renal vascular resistance in most instances. Occasional findings of a slight decrease in renal vascular resistance during a depressor response would seem to be attributed to an impairment of the general condition of animals because of the decrease in threshold stimulus strength. Since Lindgren and Uvnäs, it has been generally known that the depressor responses caused by electrical stimulation in the depressor area are accompanied by vasodilatation in the muscle and the skin.¹⁷⁾ Therefore, the renal vascular tone appears to be kept comparatively constant during the inhibition of vasoconstrictor tone of other vascular circuits on stimulation in the depressor area.

Although the dorsal vagal nuclei and the nucleus ambiguus are regarded as the chief sources of cardiac preganglionic parasympathetic fibers, no obvious findings were obtained to suggest that these nuclei participated primarily in the nervous control of the renal vessels.¹⁸⁾

In view of the present results, it is clear that under the conditions of these experiments renal blood flow is influenced not only by neural effect but also by prerenal circulatory changes. As for humoral factors, it has been shown from the previous studies by several investigators that medullary stimulation results in release of catechols from the adrenal medulla.^{19), 20)} Based on these findings, the observed variety of response patterns are reasonably explained and the results support the observation of Wise and Ganong in their view that renal vasoconstriction was not a necessary concomitant of pressor response.

While the produced patterns in central vagal stimulation are similar to those in medullary stimulation, diencephalic stimulation evoked less different effects on blood pressure and on renal blood flow. On stimulation in the diencephalon, no inhibitory influences could be caused upon the renal vascular tone. The lack of several patterns from the diencephalon may suggest the integrative activity of this area on the nervous control of the renal circulation. The present results, therefore, have indicated that diencephalic or cortical influences are probably more important than medullary ones on the nervous control of the renal circulation as on that

of other cardiovascular systems.²¹⁾ Hoff et al. already demonstrated the participation of the kidney in the vasomotor responses caused by electrical stimulation of the cortex.²²⁾

SUMMARY

(1) The influence of electrical stimulation of the medulla oblongata on the renal circulation has been investigated with a use of an electromagnetic flow meter in 40 anesthetized dogs. The stimulation evoked various responses in blood pressure and in renal blood flow.

(2) In 20 dogs, changes in renal vascular resistance, caused by medullary stimulation, were analysed by cross-perfusion experiments of the kidney.

(3) Stimulation of the lateral reticular formation evoked a rise in blood pressure with a concomitant decrease in renal blood flow. Cross-perfusion experiments revealed vasoconstriction in the perfused kidney on stimulation in this area.

(4) Stimulation in the dorsal part of the reticular formation occasionally produced an increase in renal blood flow during a pressor response. The increase in renal blood flow seemed to be passive one resulted from the elevated blood pressure.

(5) On stimulation of the medial reticular formation, renal blood flow was usually decreased with a fall in blood pressure. However, stimulation in this area generally induced no significant alteration of vascular resistance in the perfused kidney.

(6) In some dogs, stimulation in the reticular formation adjacent to the solitary tract caused a decrease in renal vascular resistance together with a pressor response, suggesting that central effects of vagal stimulation can be elicited by local stimulation of the bulb. However, this vasodilatation was not modified by vagotomy or with atropine. Stimulation of the dorsal vagal nuclei and the nucleus ambiguus did not elicit renal vasodilatation.

(7) The present study demonstrates that medullary stimulation elicits more different response patterns in blood pressure and in renal blood flow than diencephalic stimulation, although there is no evidence of active renal vasodilatation.

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