EFFECTS OF ANGIOTENSIN II ON THE MEDULLARY NEURONS AND THEIR SENSITIVITY TO ACETYLCHOLINE AND CATECHOLAMINES

Toshio SUGA, Masahiko SUZUKI and Masami SUZUKI

Department of Pharmacology, Saitama Medical School, Iruma-gun, Saitama 350-04, Japan

Accepted March 14, 1979

Abstract—In order to elucidate the mechanism of the central hypertensive action of angiotensin II (ATII), the effects of ATII on the medullary neurons of rabbits were studied by the technique of electrophoretic application. ATII gave rise to excitatory effect on some neurons of medulla and this effect was antagonized by a specific ATII antagonist, 1-sarcosine-8-alanine-ATII. The ATII sensitive medullary neurons showed no specific response to acetylcholine, norepinephrine or isoproterenol, but there was a significant increase in the excitatory response to norepinephrine in comparison with the ATII non-sensitive neurons. The excitatory effect of ATII was not blocked by atropine, phentolamine and propranolol. The ATII sensitive neurons in the medulla apparently do not have a topographically or functionally characteristic distribution related to the central vasomotor control mechanisms. The neurons in the area postrema did not respond to electrophoretically applied ATII, while microinjection of ATII in this region produced remarkable hypertensive responses. These results suggest that the mechanism of the central hypertensive action of ATII administered into the vertebral artery is primarily mediated by the chemoreception of the area postrema. The mechanism of central cardiovascular effect of ATII and of the effects of acetylcholine and catecholamines on the medullary neurons are discussed.

Since the first observation of a central effect of angiotensin II (ATII) in dogs (1), considerable evidence has accumulated that at least some of the hypertensive effects of ATII are mediated by an action on the central mechanisms of the autonomic nervous system (2). The lower medulla is considered by several investigators to be one of the sites of central hypertensive action of ATII. For example Dickinson and Yu (3) demonstrated a pressor response to a low dose of ATII infused into the vertebral artery of rabbits. Similar effects have been reported in dogs by Scroop and Lowe (4) and in humans by Ueda et al. (5). All these authors proposed that the area postrema is an important site of the action as deduced from their investigations by the methods of ablation or microinjection, considering as well that the blood-brain barrier is deficient in this region (6). To our knowledge, investigation concerning the direct action of ATII on those neurons has not been documented.

The medullary vasomotor neurons distributed widely and diffusely in the reticular formation control the central cardiovascular regulatory mechanisms (7), and autonomic nerve nuclei in the medulla such as nucleus dorsalis vagi, nucleus tractus solitarii and nucleus ambiguus control directly or indirectly the vasomotor function. Taking these topographical features and physiological function into consideration the present study concerned the direct effect of ATII on the electrical activity of the medullary neurons by
the method of electrophoretic application. Moreover, the characteristics of the AT₁₁ sensitive neurons were studied by examining responsiveness to acetylcholine (ACh), nor-
epinephrine (NE), isoproterenol (IP) and their antagonists. The mechanism of vasomotor responses to AT₁₁ in the area postrema was also investigated by combining microelectro-
phoresis and microinjection.

MATERIALS AND METHODS

Male albino rabbits weighing from 2.0 to 3.5 kg were anesthetized with ether for all surgical procedures. Cannulae were inserted into the trachea, the femoral artery and the femoral vein. After placing the rabbits in a stereotaxic instrument (Narishige SN-1), the animals were immobilized with d-tubocurarine (1.5 mg/kg i.v.) and artificially ventilated. Supplemental doses (0.5 mg/kg i.v.) of d-tubocurarine were administered as required during the course of the experiment. The foramen magnum was exposed by midline separation of the cervical musculature and removal of the allanto-occipital membrane. The dura and arachnoid were then removed. These procedures were carried out under additional local anesthesia with 1% procaine hydrochloride. The rectal temperature was kept within the range of 37–39°C by means of a heating lamp.

Glass multibarrelled micropipettes were used to record neuronal activity and to eject drugs into the vicinity of the cells. The micropipettes usually had five or seven barrels with an overall tip diameter of 5–10 μm. The recording barrel contained 3 M NaCl. One barrel always contained 1 M NaCl to apply a balancing current in order to eliminate the current effect of electrophoresis (8). The other barrels were filled with solutions of drugs. Unit discharge was led through a cathode follower (Nihon Koden MEZ-8101) to an amplifying circuit (time constant 3 msec) and displayed on an oscilloscope (Nihon Koden VC-7), from which photographic records were taken when necessary. The output from the amplifying circuit was fed through the synchronizing circuit of a stimulator (Nihon Koden SEN-1101) to a polygraph (Sanei 145), and the blood pressure, ECG and integration of the unit discharges were recorded simultaneously.

The solutions of drugs filled in the pipettes for electrophoresis were made up as follows: AT₁₁ (Protein Research Foundation, Osaka) and 1-sarcosine-8-alanine-AT₁₁ (Protein Research Foundation, Osaka): 10 mM in saline; ACh chloride (Daiichi Seiyaku), NE hydrochloride (Sigma Chemical), IP hydrochloride (Nikken Kagaku), atropine sulfate (Tokyo Kasei Kogyo), phentolamine hydrochloride (CIBA-Geigy) and propranolol hydro-
chloride (Sumitomo Chemical Industry): 1 M aqueous solution. All drugs were adjusted to a pH of 5.0–6.0. When the pH of the solution of NE and IP was adjusted, 0.2 mg/ml ascorbic acid was added to prevent the oxidation of these drugs (9).

Electrode penetration was made stereotaxically in 0.5 mm steps in the caudal brainstem in planes 0–3 mm rostral to the obex and 1–4 mm lateral to the midline. In some animals, the caudal tip of the cerebellum was removed by suction to afford direct vision of the penetration. Because it was found that electrophoretic cationic current increased the rate of firing in some neurons, as was also observed by Strumwasser and Rosenthal (10), an anionic
current was applied simultaneously to the electrophoretic cationic current to neutralize the
current effect of electrophoresis. For microinjection, AT₁ was dissolved in a concentration
of 1 mM in artificial cerebrospinal fluid (11) and adjusted to a pH of about 6. The drugs
were applied through a glass micropipette with a tip diameter of about 100 μm handled with
a micromanipulator by using a microsyringe (Thermo MS-G10) with full scale volume of
10 μl. Whole volume injected was usually less than 10 μl. The area postrema was in-
vvestigated at the lateral wall of the caudal portion of the fourth ventricle and checked in
histological sections at the end of the experiment. Some recording sites were checked in
histological sections (stained with neutral red) of the brainstem that was perfused with 10%
formalin at the end of the experiment.

RESULTS

Excitatory effect of AT₁ and antagonistic effect of L-sarcosine-8-alanine-AT₁: Micro-
electrode recording was made from 410 neurons in the caudal brainstem, most of which
showed spontaneous activity. Of these neurons, 35 units responded to AT₁ (cationic
ejection current 50–200 nA), the responses being all excitatory. The latency was variable
but usually within 20 sec. The response reached a peak in 10 to 20 sec after the application
of the drug and the after-effect lasted for several to more than 30 sec. There was a tendency
for the effect of AT₁ to reach the peak excitation in a comparatively slow manner. An
example of the effect is illustrated in Fig. 1 which shows the oscilloscope trace of a neuron
discharging spontaneously. By application of AT₁ (ejection current 200 nA) the discharge
was accelerated about 15 sec after start of the application and the acceleration lasted about
20 sec after the cessation of current. In contrast to the AT₁ effect, the excitation produced
by ACh was relatively fast at the onset as well as the termination in this case as seen in Fig. 2,
which shows the polygraphic recording of unit discharge and its integration of a neuron
which responded to both AT₁ and ACh.

Five units which showed the excitatory response to AT₁ were tested with L-sarcosine-8-

![Fig. 1. Oscilloscope recording of spontaneous unit discharge of a medullary neurons. Iontophoretic application of AT₁ (150 nA) elicited its excitation with a slow onset and with an after-effect of some duration. Vertical bar indicates 200 μV. Time marker is 1 sec.](image-url)
**FIG. 2.** Polygraphic recording of unit discharge (a) and its integration (b) of medullary neurons which responded to both AT_{11} (150 nA) and ACh (50 nA). A slow onset of action and a lasting after-effect were seen with AT_{11} application (upper), while with ACh application, a fast onset and fast cessation of action were observed (lower).

**FIG. 3.** Polygraphic recording of unit discharge (a) and its integration (b) of a medullary neuron. Excitatory effect of AT_{11} (80 nA) was blocked by simultaneous application of SA-AT_{11} (150 nA).

**FIG. 4.** Polygraphic recording of electrocardiogram (ECG), blood pressure (BP), unit discharge (UD) of a type 2 vasomotor neuron and its integration (IUA). AT_{11} (150 nA) elicited the excitatory effect on the neuron which showed depressed neuronal activity in the case of the elevation of blood pressure following i.v. administration of epinephrine (2.5 μg/kg).
alanine-AT\textsubscript{II} (SA-AT\textsubscript{II}), a specific AT\textsubscript{II} antagonist. When SA-AT\textsubscript{II} was applied simultaneously with AT\textsubscript{II} in a dose of 2 or 3 times as much as that of AT\textsubscript{II} (12), the excitatory effects of AT\textsubscript{II} were more or less depressed during the application of SA-AT\textsubscript{II} (Fig. 3).

Vasomotor neurons were identified according to the criterion presented by Hukuhara and Takeda (7). Type 1 vasomotor neurons increased the spontaneous unit discharge during the period of decrease of the renal nerve discharge, as in the case where the blood pressure was elevated by i.v. administration of epinephrine. Type 2 neurons showed the opposite direction of change in the unit discharge. An example of the excitatory effect of AT\textsubscript{II} on the type 2 neuron is shown in Fig. 4. The numbers of vasomotor- and the AT\textsubscript{II} sensitive neurons among the neurons observed are summarized in Table 1. The rate of responses of the vasomotor neurons to AT\textsubscript{II} was not significantly different from that of the non-vasomotor neurons. Respiratory neurons did not respond to AT\textsubscript{II}. The AT\textsubscript{II} sensitive neurons were distributed diffusely in the medulla and there was no characteristic localization related to central vasomotor control mechanisms (Fig. 5).

**Fig. 5.** Localization of AT\textsubscript{II} sensitive medullary neurons plotted in the rabbit brain atlas by Meessen and Alszewski (13). AT\textsubscript{II} sensitive neurons scattering diffusely in the structure of the medulla where no characteristic localization of the AT\textsubscript{II} sensitive neurons could be found. A, B and C are the frontal sections at level of 1, 2 and 3 mm rostral from the obex, respectively. Abbreviations; Al, nucleus alaris; Ao, nucleus ambiguous oralis; Cul, nucleus cuneatus lateralis; Cum, nucleus cuneatus medialis; Flp, fasciculus longitudinalis posterior; Gr, nucleus gracilis; Lcmc, subnucleus lateralis caudalis magnocellularis; NRVIII, nucleus radialis descendens nervi vestibularis; Nts, nucleus tractus solitarii; NV, nucleus tractus spinalis trigemini; NXII, nucleus nervi hypoglossi; Pg, promontorium gliosum; pOL, nucleus paraovalis medialis; pOld, nucleus paraovalis dorsalis; Prph, nucleus praepositus hypoglossi; Rgc, nucleus reticularis gigantocellularis; R1, nucleus reticularis lateralis; Rpc, nucleus reticularis parvocellularis; RV, subnucleus reticularis ventralis; Trg, nucleus triangularis; Ts, tractus solitarius.
TABLE 1. \( \text{AT}_{11} \) sensitivity of vasomotor and non-vasomotor neurons

|                      | Vasomotor neuron | Non-vasomotor neuron | Total |
|----------------------|------------------|----------------------|-------|
| \( \text{AT}_{11} \) sensitive neuron | 2/28 | 6/62 | 8/80 | 27/375 | 35/375 |
| \( \text{AT}_{11} \) non-sensitive neuron | 6/72 | 34/146 | 40/216 | 335/1375 | 375/1375 |
| Total                | 8/80 | 40/216 | 48/296 | 362/1750 | 410/1750 |

\( \chi^2 \) 3.30 2.73

No statistically significant difference was found in the number of \( \text{AT}_{11} \) sensitive neurons between vasomotor and non-vasomotor neurons.

TABLE 2. Responses of \( \text{AT}_{11} \) sensitive neurons to ACh, NE and IP

|                      | \( \text{AT}_{11} \) sensitive neuron | \( \text{AT}_{11} \) non-sensitive neuron | \( \chi^2 \) |
|----------------------|--------------------------------------|----------------------------------------|------------|
| Acetylcholine        | 3/5 (44.4)                           | 7/11 (25.9)                           | 1.09       |
| Excitatory Norepinephrine | 4 (27.8)                       | 4 (7.3)                               | 6.54*      |
| Isoproterenol        | 3/5 (36.4)                           | 7/11 (13.3)                           | 0.69       |
| Acetylcholine        | 2/5 (42.2)                           | 8/12 (29.6)                           | 0.18       |
| Inhibition Norepinephrine | 6 (38.9)                        | 32/5 (58.2)                           | 2.05       |
| Isoproterenol        | 3/5 (27.3)                           | 9/13 (30.0)                           | 0.03       |
| Acetylcholine        | 4/5 (33.3)                           | 12/13 (44.4)                          |           |
| No response Norepinephrine | 8/10 (33.3)                    | 19/13 (34.5)                          |           |
| Isoproterenol        | 5/5 (36.4)                           | 14/13 (13.3)                          |           |

*The increase in the rate of excitatory response of \( \text{AT}_{11} \) sensitive neurons to NE in comparison with \( \text{AT}_{11} \) non-sensitive neurons was significant (P = 0.05).

\( \text{AT}_{11} \) sensitive neurons and the effects of ACh, NE and IP: In this experiment, the \( \text{AT}_{11} \) sensitive neurons were investigated to determine the relationship between the responsiveness to \( \text{AT}_{11} \) and those to ACh, NE and IP. ACh, NE and IP were ejected by a cationic current of 10-50 nA. These drugs produced both excitatory and inhibitory responses in frequencies as seen in Table 2. The excitatory response began within the first 5 sec and the rate of firing reached a peak in 5 to 20 sec after the application of drugs. The after-effect lasted for 3 to 20 sec. The inhibitory response began within the first 5 sec and reached a peak in 5 to 20 sec after the application of the drug. Here the after-effect lasted for 3 to 30 sec (Figs. 6, 7). When the correlation of the response between \( \text{AT}_{11} \) and ACh, NE or IP was investigated by \( \chi^2 \) test, increase in the excitatory effect of NE on \( \text{AT}_{11} \) sensitive neurons was found to be significant.

Effects of atropine, phentolamine and propranolol on the responses to \( \text{AT}_{11} \), ACh, NE and IP: Table 3 summarizes the results concerning the effects of atropine, phentolamine and propranolol on the responses elicited by \( \text{AT}_{11} \), ACh, NE and IP in the medullary neurons. The excitatory effect of \( \text{AT}_{11} \) was not affected by simultaneous application of atropine, phentolamine and propranolol. The effects of ACh, both excitation and inhibition, were
The excitatory effect of NE was blocked by phentolamine in most cases (3 of 5 experiments), but unaffected by other blockers. Inhibitory effect of NE was decreased in a few cases (2 of 7 experiments) by phentolamine, but not by other blockers. The excitatory effect of IP was blocked by atropine, but were unaffected by phentolamine and propranolol. The excitatory effect of NE was blocked by phentolamine in most cases (3 of 5 experiments), but unaffected by other blockers. Inhibitory effect of NE was decreased in a few cases (2 of 7 experiments) by phentolamine, but not by other blockers. The excitatory effect of IP was blocked by...
propranolol in most cases and blocked by phentolamine in some cases (2 of 5 experiments), but was unaffected by atropine. Inhibitory effect of IP was blocked by propranolol in only one case, but was unaffected by other blockers. Atropine and phentolamine showed inhibitory effects on the spontaneous activity of some medullary neurons. The inhibitory effects produced by atropine and phentolamine were not the ones mediated by their actions on the effects of ACh and NE (Fig. 8). Thus, the effects of agonists and antagonists on the medullary neurons were considerably diverse in comparison with those on the peripheral

**TABLE 3. Effects of propranolol, phentolamine and atropine on responses of medullary neurons to AT1i, ACh, NE and IP**

| Response | Angiotensin II | Acetylcholine | Norepinephrine | Isoproterenol |
|----------|----------------|---------------|----------------|--------------|
|          | Excitation     | Inhibition    | Excitation     | Inhibition   |
|          | Propranolol    | Phenolamine   | Propranolol    | Phenolamine |
|          | 0              | 0             | 0              | 0            |
|          | 5              | 5             | 5              | 5            |
|          | 0              | 0             | 3              | 4            |
|          | 4              | 4             | 2              | 4            |
|          | 0              | 0             | 2              | 5            |
|          | 4              | 4             | 3              | 4            |
|          | 0              | 3             | 0              | 4            |
|          | 4              | 2             | 4              | 4            |
|          | 0              | 2             | 0              | 5            |
|          | 2              | 3             | 4              | 4            |
|          | 0              | 1             | 0              | 4            |
|          | 3              | 4             | 4              | 4            |

**Fig. 8.** Polygraphic recording of unit discharges of two medullary neurons (a) and the integrations (b). Atropine (ATR, 50 nA) elicited an inhibitory effect on one neuron on which ACh (50 nA) induced no effect. Phenolamine (PHEN, 50 nA) elicited an inhibitory effect on the other neuron on which NE (50 nA) induced an inhibitory effect. ATR (50 nA) had no effect on this neuron.
Effects of ATII on the area postrema: With electrophoretic application, the direct effect of ATII was investigated in more 40 neurons of the area postrema from the dorsal surface of the medulla. Neither spontaneously active nor silent neurons responded to ATII applied electrophoretically. However, the microinjection of ATII in a dose of more than 2 nmol brought about a considerably lasting elevation of blood pressure, which was dose-dependent (Fig. 9). Microinjection of artificial cerebrospinal fluid elicited no response. The locus which responded to ATII was restricted to the area postrema and other loci even slightly lateral or rostral from area postrema did not respond to the microinjection.

**DISCUSSION**

The present investigation of the behavior of ATII sensitive neurons in the lower brainstem of rabbits was made on the basis of the presence of vasomotor neurons and of some nuclei related to the central vasomotor control mechanism in the medulla. It was thus found that certain ATII sensitive neurons in the medulla showed an excitatory response to the electrophoretic application of ATII, and that excitatory effects of ATII are antagonized by simultaneous application of SA-ATII. This means that the excitatory effect is due to a specific action of ATII on the neurons (12, 14). There have been several reports (15-17) identifying the medulla as a site of the central hypertensive action of ATII when such is given into the vertebral artery. Most of those workers proposed that the area postrema is an important site of action, in view of the results using ablation or microinjection methods.
and in consideration of the fact that the blood-brain barrier is deficient in the area (6). On the other hand, Hoffman and Phillips (18) reported that the most sensitive site of the hypertensive effect of \( \text{AT}_{1/2} \) was the ventral anterior third ventricle or perivascular tissue surrounding it and that the hypertensive effect was not apparent when \( \text{AT}_{1/1} \) was applied to the fourth ventricle. Although it has been reported that renin and angiotensin are endogenous (19, 20) and that angiotensin in the dog brain is concentrated in the brainstem (19), this octapeptide is apparently not directly concerned with central vasomotor control mechanisms in the medulla, as in experiment, \( \text{AT}_{1/1} \) sensitive neurons showed no characteristic localization.

No neuron in the area postrema responded to electrophoretic application of \( \text{AT}_{1/1} \), while the microinjection of \( \text{AT}_{1/1} \) in the region elicited a remarkable blood pressure elevation. The latter results were the same to that reported by Ueda et al. (17). Loci other than the area postrema did not respond to microinjection of \( \text{AT}_{1/1} \). In previous work (21) we found that the infusion of \( \text{AT}_{1/1} \) into the vertebral artery brought about an increase in the unit discharge of the type 2 vasomotor neuron (relation with vasopressor function) and a decrease in the discharge of the type 1 neuron (relating with vasodepressor function) immediately before the blood pressure elevation. Thus, it is suggested that the intra-arterially or intravenously administered \( \text{AT}_{1/1} \) stimulates a chemoreceptor in the blood vessel wall of the area postrema which in turn activates central vasomotor control mechanisms in the medulla before the direct action of \( \text{AT}_{1/1} \) on the medullary neurons. It seems that \( \text{AT}_{1/1} \) does not act directly on the neurons in the area postrema after passing through the blood-brain barrier, as no neuron responded to the electrophoretically applied \( \text{AT}_{1/1} \).

\( \text{AT}_{1/1} \) sensitive medullary neurons were found to have no certain specific sensitivity to ACh, NE or IP. However, the number of neurons which elicited excitatory responses to NE was larger in \( \text{AT}_{1/1} \) sensitive neurons than in \( \text{AT}_{1/1} \) non-sensitive neurons, as determined statistically. Considerable evidence has accumulated for the hypotensive action of \( \alpha \)-adrenergic stimulants and \( \beta \)-adrenergic blockers as the result of central mechanisms (22-24). In our experiments, no correlation of responses to the adrenergic agonists with those to the antagonists could be found in \( \text{AT}_{1/1} \) sensitive neurons. Furthermore, although the central hypertensive effect of \( \text{AT}_{1/1} \) administered into the vertebral artery is reportedly blocked by pre-administration of atropine (4), the effect of electrophoretically applied \( \text{AT}_{1/1} \) on the medullary neurons was not blocked by simultaneous electrophoretic application of atropine. The effects of catecholamines, ACh and their antagonists on the medullary neurons were diverse and considerably different from such effect on peripheral tissues. Moreover, the relation between the direct effects of these monoamines on the medullary neurons and their cardiovascular effects mentioned above is not well established.

There have been discrepancies in the results concerning the responsiveness of the medullary neurons to electrophoretically applied catecholamines and ACh (25-28). In the present experiment, the pH of the solution for amines and \( \text{AT}_{1/1} \) was adjusted to about 6.0, because the larger the pH, the greater was the effect. At least the excitatory effect caused by \( H^+ \) in acidic solution (29) could be avoided by adjustment of the pH. The effect of pH observed in our study seems to be related with the passage of applied drugs through the
synaptic barrier of neurons (30), the mechanism of which awaits elucidation.

Acknowledgement: We are grateful to Hoan-sha for financial support in this investigation.

REFERENCES

1) Bickerton, R.K. and Buckley, J.P.: Evidence for a central mechanism in angiotensin-induced hypertension. Proc. Soc. exp. Biol. Med. 106, 834–836 (1961)
2) Severs, W.B. and Daniel-Severs, A.E.: Effects of angiotensin on the central nervous system. Pharmacol. Rev. 25, 415–449 (1973)
3) Dickerson, C.J. and Yu, R.: Mechanism involved in the progressive pressor response to very small amount of angiotensin in conscious rabbits. Circulation Res. 21, Supp. 2, 157–163 (1967)
4) Scroop, G.C. and Lowe, R.D.: Central pressor effect of angiotensin mediated by the parasympathetic nervous system. Nature 200, 1331–1332 (1968)
5) Ueda, H., Uchida, Y., Ueda, K., Gondaira, T. and Katayama, S.: Centrally mediated effect of angiotensin in man. Japan. Heart J. 10, 243–247 (1969)
6) Wilson, G.M.W. and Brodie, B.B.: The absence of blood-brain barrier from certain areas of the central nervous system. J. Pharmacol. exp. Ther. 133, 332–334 (1961)
7) Hukuhara, T. Jr. and Takeda, R.: Neuronal organization of central vasomotor control mechanism in the brain stem of the cat. Brain Res. 87, 419–429 (1975)
8) Salmoiraghi, G.C. and Weight, F.: Micromethods in neuropharmacology: an approach to the study of anesthesia. Anesthesiol. 28, 54–64 (1967)
9) Zarzechi, P., Blak, D.J. and Somjen, G.G.: Interactions of nigrostriate synaptic transmission, iontophoretic O-methylated phenethylamines, dopamine, apomorphine and ACh. Brain Res. 115, 257–272 (1976)
10) Strumwasser, F. and Rosenthal, S.: Prolonged and patterned direct extracellular stimulation of single neurons. Am. J. Physiol. 198, 405–413 (1960)
11) Leusen, I.: The influence of calcium, potassium and magnesium ions in cerebrospinal fluid on the vasomotor system. J. Physiol. 110, 319–329 (1950)
12) Phillips, M.I. and Felix, D.: Specific angiotensin II receptive neurons in the cat subfornical organ. Brain Res. 109, 531–540 (1976)
13) Meessen, H. and Olszewski, J.: Cytarchitecturarischer Atlas des Rautenhirns des Kaninchens. Karger, Basel (1949)
14) Regoli, D., PARK, W.K. and Rioux, F.: Pharmacology of angiotensin. Pharmacol. Rev. 26, 69–124 (1974)
15) Scroop, G.C., Katic, F., Joy, M.D. and Lowe, R.D.: Importance of central vasomotor effects in angiotensin-induced hypertension. Brit. med. J. 1, 324–326 (1971)
16) Joy, M.D. and Lowe, R.D.: Evidence that the area postrema mediates the central cardiovascular response to angiotensin II. Nature 228, 1303–1304 (1970)
17) Ueda, H., Katayama, S. and Kato, R.: Area postrema—angiotensin-sensitive site in brain. Adv. exp. Biol. Med. 17, 109–116 (1972)
18) Hoffman, W.E. and Phillips, M.I.: Regional study of cerebral ventricle sensitive site to angiotensin II. Brain Res. 101, 313–330 (1976)
19) Fischer-Ferrario, C., Nahmod, V.E., Goldman, D.J., and Finkelman, S.: Angiotensin and renin in rat and dog brain. J. exp. Med. 133, 353–361 (1971)
20) Ganten, D., Minich, J., Granger, P., Hayduk, K., Brecht, H.M., Barbeau, R., Boucher, R. and Genest, J.: Angiotensin forming enzyme in brain tissue. Science 173, 64–65 (1971)
21) Sakai, Y. and Suga, T.: Effect of angiotensin II on the vasomotor unit activity in the medulla oblongata. Japan. J. Pharmacol. 25, Supp. 184 P (1975)
22) Bhargava, K.P., Mischra, N. and Tangri, K.K.: An analysis of central adrenoceptors for control of cardiovascular function. Brit. J. Pharmacol. 45, 596–602 (1972)
23) Srivastava, R.K., Kursiretha, V.K., Singh, N. and Bhargava, K.P.: Central cardiovascular effects of intracerebroventricular propranolol. Europ. J. Pharmacol. 21,
222–229 (1973)

24) Day, M.D. and Roach, A.G.: Central α- and β-adrenoceptors modifying arterial blood pressure and heart rate in conscious cats. Brit. J. Pharmacol. 51, 321–333 (1974)

25) Curtis, D.R. and Koizumi, D.R.: Chemical transmitter substances in the brain stem of cat. J. Neurophysiol. 24, 80–90 (1961)

26) Bradley, P.B. and Wolstencroft, J.H.: Excitation and inhibition of brainstem neurons by noradrenaline and acetylcholine. Nature 196, 840 and 873 (1962)

27) Salmoiraghi, G.C. and Steiner, F.A.: Acetylcholine sensitivity of cat medullary neurons. J. Neurophysiol. 26, 581–597 (1963)

28) Boakes, R.J., Bradley, P.B., Boakes, N., Candy, J.M. and Wolstencroft, J.H.: Action of noradrenaline, other sympathomimetic amines and antagonists on neurons in the brainstem of the cat. Brit. J. Pharmacol. 41, 462–479 (1971)

29) Krnjevic, K. and Phillips, J.W.: Iontophoretic studies of neurons in the mammalian central cortex. J. Physiol. 165, 274–304 (1963)

30) Curtis, D.R. and Eccles, R.M.: The excitation of Renshaw Cells by pharmacological agents applied electrophoretically. J. Physiol. 141, 435–445 (1958)