RECENT TRENDS IN THE NEUROPHARMACOLOGY OF CENTRAL VASOMOTOR LOCI

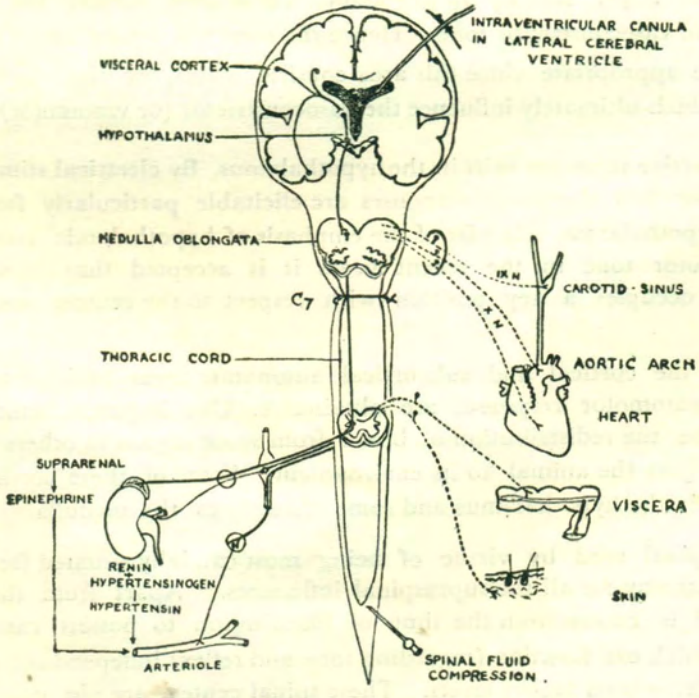
by

K. P. BHARGAVA

Department of Pharmacology, K. G. Medical College, Lucknow.

The importance of the central nervous system in the control of autonomic function is now well established. The autonomic nervous system is no longer considered to be a purely efferent system. For example, in the nervous regulation of the tone of blood vessels afferent, central and efferent factors participate.

The most important afferents concerned in the regulation of vascular tone are those arising from the carotid and aortic sinuses. They are mainly inhibitory in their function. During recent years other visceral afferents have been discovered which play quite an important part in the reflex regulation of blood pressure.



BLOOD PRESSURE REGULATION

The so called vasomotor "center" is principally situated in the reticular formation of the medulla oblongata. Several workers have charted the whole medulla oblongata (in cat) with respect to blood pressure changes by using the topical stimulation by the Horsley-Clark Stereotaxic technic. Rises of blood pressure were obtained from lateral portions of lateral reticular formation whereas blood pressure falls were mostly elicited from the caudal part of the medial reticular formation. Ranson and Billingsley in 1916 described two superficial points in the floor of the fourth ventricle from where pressor and depressor responses were obtained. This gave rise to the concept of a vasonconstrictor and vasodilator center. These two centers were assumed to have reciprocal actions, so that pressor reflex, for example involved primarily an increase of vasoconstrictor tone and a depressor reflex implied primarily an increase of vasodilator tone. The dual theory has been subscribed to by many investigators including Bayliss. It has, however, been much criticized by several later authors. What, then, is the mechanism in depressor reflex mediated via the medulla oblongata or in direct stimulation of the vasodilator center since in both these instances generalised vasodilation in unquestionably produced ? This vasodilation is brought about only by inhibition of vasoconstrictor tone via the medullary vasoconstrictor center. It seems incorrect, however, to use the designation "vasodilator center", since the activity therein does not imply activity in any known vasodilator nerves, but merely inhibition of vasoconstrictor tone. Hence the term "depressor area" appears to be more appropriate since this area consists mainly of the "depressor" afferents which ultimately influence the vasoconstrictor (or vasomotor) center.

Vaso-active neurones exist in the hypothalamus. By electrical stimulation both pressor and depressor responses are elicitable particularly from the anterior hypothalamus. Inspite of the emphasis of hypothalamic control of the vasomotor tone in the recent years it is accepted that the medulla oblongata occupies a key position with respect to the central vasomotor control.

From the cortical and subcortical autonomic areas both pressor and depressor vasomotor responses are obtainable. One important function of these may be the redistribution of blood from some organs to others with a view to adjust the animal to its environment. Some of these corticofugal fibers run via the hypothalamus and some directly to the medulla.

The spinal cord by virtue of being most caudally situated forms the common pathway for all the supraspinal influences. Apart from this, the spinal cord is known from the time of Sherrington to possess vasomotor neurones which can function (regarding tone and reflex) independant of the excitatory drive from higher levels. These spinal centers are not considered

to play any appreciable role in the maintenance of the vasomotor tone under normal conditions.

The major efferents concerned in vasomotor tone are the sympathetic adrenergically mediated vasoconstrictor influences. Despite the existence of several cholinergic vasodilator systems, it is generally agreed that these do not play any significant role in the maintenance of the normal "tonus" of blood vessels.

The largest group of drugs known to modify blood pressure act on the peripheral efferent outflow e. g. the ganglion and adrenergic blocking agents. Only a few act on the afferent system e. g. veratum and very few are known to directly modify the activity of the center.

Since the discovery of the specific central action of Rauwolfia in lowering blood pressure (Bhargava and Borison, 1955; 1957), I became interested in the investigation of the central site of action of a series of hypotensive drugs. Commonly, if an agent produces hypotension and it is shown to possess adrenergic or ganglion blocking properties an additional (and often more important) central locus of action is not considered. The problem of finding out an additional central site of action is difficult, since the possible central action is ordinarily masked by the peripheral (ganglionic or adrenergic) blockade (Dontas and Nickerson, 1956).

We had to devise suitable technics by which the central hypotensive action could be studied independant of the peripheral action. We have investigated the central vasomotor effects of some ganglion blocking agents (viz. pempidine, mecamylamine, tetra-ethylammonium, hexamethonium, pentolinium and chlorisondamine) and certain adrenergic blocking agents (viz. hydralazine, chlorpromazine, yohimbine, rauwolscine, tolazoline, hydergin, and ergotamine). The study was done in dogs and cats anaesthetised with pentobarbital sodium, vagotomised and maintained on artificial respiration. Throughout the study, control ganglionic response or epinephrine response was elicited to guard against the peripheral action of the agents.

The activity of the supra-spinal vasomotor centers was assessed by (i) the *reflexly* mediated vasomotor responses viz., the carotid occlussion pressor response or the pressor/depressor response evoked by electrical stimulation of the central cut end of vagus and (ii) the vasomotor response evoked by *direct* electrical stimulation of the vasomotor center by means of the Horseley-Clarke stereotaxic technic. The effect of drugs on the spinal vasomotor loci was studied by eliciting the vasomotor responses to intrathecal compression of the spinal cord in cats (with spinal cord ligated at C_7 within the meninges). The technic of eliciting the spinal compression vasomotor response

proved to be a very useful tool for the investigation of drugs acting at the spinal level (Bhargava and Kulsreshtha, 1959).

I shall now briefly describe the various procedures of injection of the drug adopted in the study. *Intravertebral injection* was made by means of a thin polythene tube introduced into a vertebral artery at its origin from the subclavian artery. The subclavian artery distal to the origin of the vertebral was ligated. By this means a small amount of the drug could be localised in the vasomotor centers and their reflex excitability observed. However, peripheral leakage after a short time, in this procedure could not be avoided.

Intracerebroventricular injection was made by means of a polythene cannula introduced into a lateral cerebral ventricle through a burr hole in the cranium. The hole was tightly sealed and pulsations of the CSF could be seen in the outer portion of the transparent cannula. This technic was very successful in localising the drug in the central nervous system; peripheral leakage was rare. Effect of such an injection on the reflex cardiovascular response indicated the action at the central site. (Bhargava and Tangri, 1960)

Injection into isolated head-circulation was achieved by the cross-circulation technic. The head circulation of a recepient dog was maintained by a donor dog. The circulation in the head was thus cut off from the circulation in the body of the recepient yet the nervous connections between the head and the body remained intact. The drug could thus be introduced into the head and its effects (through the nerves) could be observed in the body circulation. The technic was quite laborious and an absolute separation of the two circulations was difficult to acheive.

Intravenous injection of the drug was made through a polythene cannula introduced into a femoral vein. The obvious objection to this route was the peripheral distribution of the drug, but in some cases a dose could be found out which was insufficient for eliciting the peripheral effects and the direct central vasomotor excitability was appreciably altered.

Of the ganglion blocking agents investigated pempidine had a central vasomotor stimulant action, (Dhawan and Bhargava, 1960). Mecamylamine, hexamethonium and TEA had a central depressant action and pentolinium and chlorisondamine were found to be devoid of any central action. All of the adrenergic blocking agents investigated possessed an additional central hypotensive action.

Hydralazine had a definite central hypotensive action in a dose which did not produce adrenergic block (Tangri and Bhargava, in Press). Chlorp-

to play any appreciable role in the maintenance of the vasomotor tone under normal conditions.

The major efferents concerned in vasomotor tone are the sympathetic adrenergically mediated vasoconstrictor influences. Despite the existence of several cholinergic vasodilator systems, it is generally agreed that these do not play any significant role in the maintenance of the normal "tonus" of blood vessels.

The largest group of drugs known to modify blood pressure act on the peripheral efferent outflow e. g. the ganglion and adrenergic blocking agents. Only a few act on the afferent system e. g. veratum and very few are known to directly modify the activity of the center.

Since the discovery of the specific central action of Rauwolfia in lowering blood pressure (Bhargava and Borison, 1955; 1957), I became interested in the investigation of the central site of action of a series of hypotensive drugs. Commonly, if an agent produces hypotension and it is shown to possess adrenergic or ganglion blocking properties an additional (and often more important) central locus of action is not considered. The problem of finding out an additional central site of action is difficult, since the possible central action is ordinarily masked by the peripheral (ganglionic or adrenergic) blockade (Dontas and Nickerson, 1956).

We had to devise suitable technics by which the central hypotensive action could be studied independant of the peripheral action. We have investigated the central vasomotor effects of some ganglion blocking agents (viz. pempidine, mecamylamine, tetra-ethylammonium, hexamethonium, pentolinium and chlorisondamine) and certain adrenergic blocking agents (viz. hydralazine, chlorpromazine, yohimbine, rauwolscine, tolazoline, hydergin, and ergotamine). The study was done in dogs and cats anaesthetised with pentobarbital sodium, vagotomised and maintained on artificial respiration. Throughout the study, control ganglionic response or epinephrine response was elicited to guard against the peripheral action of the agents.

The activity of the supra-spinal vasomotor centers was assessed by (i) the *reflexly* mediated vasomotor responses viz., the carotid occlussion pressor response or the pressor/depressor response evoked by electrical stimulation of the central cut end of vagus and (ii) the vasomotor response evoked by *direct* electrical stimulation of the vasomotor center by means of the Horseley-Clarke stereotaxic technic. The effect of drugs on the spinal vasomotor loci was studied by eliciting the vasomotor responses to intrathecal compression of the spinal cord in cats (with spinal cord ligated at C_7 within the meninges). The technic of eliciting the spinal compression vasomotor response

proved to be a very useful tool for the investigation of drugs acting at the spinal level (Bhargava and Kulsreshtha, 1959).

I shall now briefly describe the various procedures of injection of the drug adopted in the study. *Intravertebral injection* was made by means of a thin polythene tube introduced into a vertebral artery at its origin from the subclavian artery. The subclavian artery distal to the origin of the vertebral was ligated. By this means a small amount of the drug could be localised in the vasomotor centers and their reflex excitability observed. However, peripheral leakage after a short time, in this procedure could not be avoided.

Intracerebroventricular injection was made by means of a polythene cannula introduced into a lateral cerebral ventricle through a burr hole in the cranium. The hole was tightly sealed and pulsations of the CSF could be seen in the outer portion of the transparent cannula. This technic was very successful in localising the drug in the central nervous system; peripheral leakage was rare. Effect of such an injection on the reflex cardiovascular response indicated the action at the central site. (Bhargava and Tangri, 1960)

Injection into isolated head-circulation was achieved by the cross-circulation technic. The head circulation of a recepient dog was maintained by a donor dog. The circulation in the head was thus cut off from the circulation in the body of the recepient yet the nervous connections between the head and the body remained intact. The drug could thus be introduced into the head and its effects (through the nerves) could be observed in the body circulation. The technic was quite laborious and an absolute separation of the two circulations was difficult to acheive.

Intravenous injection of the drug was made through a polythene cannula introduced into a femoral vein. The obvious objection to this route was the peripheral distribution of the drug, but in some cases a dose could be found out which was insufficient for eliciting the peripheral effects and the direct central vasomotor excitability was appreciably altered.

Of the ganglion blocking agents investigated pempidine had a central vasomotor stimulant action, (Dhawan and Bhargava, 1960). Mecamylamine, hexamethonium and TEA had a central depressant action and pentolinium and chlorisondamine were found to be devoid of any central action. All of the adrenergic blocking agents investigated possessed an additional central hypotensive action.

Hydralazine had a definite central hypotensive action in a dose which did not produce adrenergic block (Tangri and Bhargava, in Press). Chlorp-

romazine had a more important central vasomotor depressant action than the peripheral effect. The central action has been localised to be in the hypothalamic region (Tangri and Bhargava, in Press).

REFERENCES.

Bhargava, K. P. and Borison, H. L. (1955) : *J. Pharmacol. & Exper. Therap.*, **115**, 464.

Bhargava, K. P. and Borison, H. L. (1957) : *J. Pharmacol. & Exper. Therap.*, **119**, 395.

Bhargava, K. P. and Kulsreshtha, J. K. (1959) : *Arch. int. Pharmacodyn.*, **120**, 85.

Bhargava, K. P. and Tangri, K. K. (1959) : *Brit. J. Pharmacol.*, **14**, 411.

Dhawan, K. N. and Bhargava, K. P. (1960) : *Brit. J. Pharmacol.*, **15**, 222.

Dontas, A. S. and Nickerson, M. (1956) : *Arch. int. Pharmacodyn.*, **106**, 312.

Ranson, S. W. and Billingsley, P. R. (1916) : *Amer. J. Physiol.*, **40**, 571.

Tangri, K. K. and Bhargava, K. P. (1960) : *Arch. int. Pharmacodyn., in Press.*