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PRESSOR RESPONSE INDUCED BY LOCAL ANAESTHETICS PERFUSED THROUGH THE CEREBRAL VENTRICLES OF DOGS

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1 The antihistamines mepyramine and halopyramine which have local anaesthetic properties, produced a rise in arterial blood pressure followed by a fall, similar to that seen with procaine, when perfused in a 10 mg/ml solution from the lateral ventricle to the cisterna magna in dogs.

2 The pressor response produced by procaine perfused through the cerebral ventricle is due to an action on structures situated in the caudal half of the floor of the fourth ventricle because a pressor response was obtained when a few microlitres of a 50 mg/ml solution of procaine were applied to a small area of the exposed floor of the fourth ventricle in a region 2 to 4 mm rostral to obex, and after cauterization of this area procaine perfused through the cerebral ventricles no longer raised arterial blood pressure.

3 Bilateral denervation of the carotid sinus did not affect the pressor response obtained with procaine perfused through the cerebral ventricles.

4 The pressor response to procaine is mediated through the sympathetic nervous system. It results partly from an increased adrenaline discharge from the adrenal glands and partly from increased sympathetic vasomotor tone, because the response is abolished or attenuated after removal of the adrenal glands and intravenous injections of hexamethonium and phentolamine.

Introduction

Procaine, injected or perfused into the cerebral ventricles of unanaesthetized dogs or anaesthetized dogs and cats, was shown to produce a biphasic blood pressure response, i.e. an initial rise followed by a fall in arterial blood pressure (Haranath, Naseem-Ayesha-Begum & Sitaramayya, 1965; Haranath & Venkatakrishna-Bhatt, 1968a; Borison, Haranath & McCarthy, 1972). Similar results were obtained with two other local anaesthetics, cinchocaine and lidocaine (Haranath & Venkatakrishna-Bhatt, 1968b), as well as with propranolol which also has local anaesthetic properties. The results with propranolol were obtained on its injection into the cerebral ventricles of anaesthetized dogs (Shrivastava, Kulshrestha, Singh & Bhargava, 1973) and of unanaesthetized rabbits (Dollery, Lewis, Myers & Reid, 1973) and cats (Day & Roach, 1974).

An initial rise followed by a fall would thus appear to be the characteristic blood pressure response to local anaesthetics when they are injected into or perfused through the cerebral ventricles. This suggestion is supported by the present experiments in which the same response was obtained with two antihistamines, mepyramine and halopyramine, that have local anaesthetic properties.

Further experiments deal with the site at which procaine acts when producing its pressor effect. Previous experiments suggested structures in the distal half of the floor of the fourth ventricle as the site because the response occurred on perfusion of the cerebral ventricles when the procaine was prevented from entering the lateral ventricles, the third and the rostral half of the fourth ventricle (Haranath *et al.*, 1965) whereas no pressor response was obtained when the procaine was perfused through the subarachnoid space surrounding the brain stem (Haranath & Venkatakrishna-Bhatt, 1968a). The procedure adopted in the present experiments for localizing the site of action in the distal half of the floor of the fourth ventricle was to apply the procaine topically to small areas of the exposed floor and to show that its intraventricular injection no longer produced a rise in arterial blood pressure when the area from which a pressor response had been obtained on topical application was cauterized. Finally, in order to find out if the pressor response was due to blockade of impulses from the carotid sinus nerves and if it resulted from activation of the sympathetic nervous system, the effects of denervation of the carotid sinus, of removal of the suprarenals and of intravenous injections of

hexamethonium and phentolamine on the pressor response were examined.

Methods

Dogs weighing 5.5 to 15 kg were used. They were anaesthetized with intravenous chloralose (100 mg/kg). The blood pressure was recorded from the cannulated right femoral artery with a mercury manometer, and the drugs were injected into the cannulated right femoral vein. The trachea was cannulated so that artifical ventilation could be applied when necessary.

For the perfusion of the cerebral ventricles, from the left lateral ventricle to the cisterna magna, the method used was that described for cats by Bhattacharya & Feldberg (1958). The rate of perfusion was 0.1 ml/minute.

For the topical application of procaine to small areas of the distal half of the floor of the fourth ventricle and for cauterization of these areas the cisterna magna was opened by cutting away the exposed atlanto-occipital membrane and enlarging the opening by nibbling away the occipital bone which forms the rostral margin of the cisterna. The cerebellum was then elevated with a spatula. The procaine solution (50 mg/ml) was applied with a fine polyethylene tube PE 10 attached to a AGLA brand micrometer syringe (B.W.Co) which is capable of delivering fractions of a microlitre. Gentle cauterization was used to produce discrete lesions in different parts of the distal half of the floor of the fourth ventricle and the side of the medulla. A thermal cautery heated to turn cotton wool brown on contact was used for this purpose. In one experiment the area postrema was cauterized on both sides under aseptic conditions. The success of the ablation was tested functionally seven days later by intravenous apomorphine which no longer produced emesis. The dog was then anaesthetized with chloralose and the cerebral ventricles were perfused with procaine.

To denervate the carotid sinus, the tissue behind the bifurcation of the carotid artery, excluding the internal and external carotid artery, was cut between two mass ligatures. To remove the adrenal glands the paravertebral retroperitoneal approach was used.

Drugs

The following drugs were used: procaine hydrochloride (May & Baker), mepyramine maleate (May & Baker) (the concentrations given for these drugs refer to their salts), halopyramine (Synopen of Suhrid Geigy) and phentolamine (Regitine, Ciba). The composition of the artificial cerebrospinal fluid (c.s.f.) used for perfusion of the cerebral ventricles and the method of preparing the isotonic solution of procaine hydrochloride were the same as described previously (Haranath *et al.*, 1965).

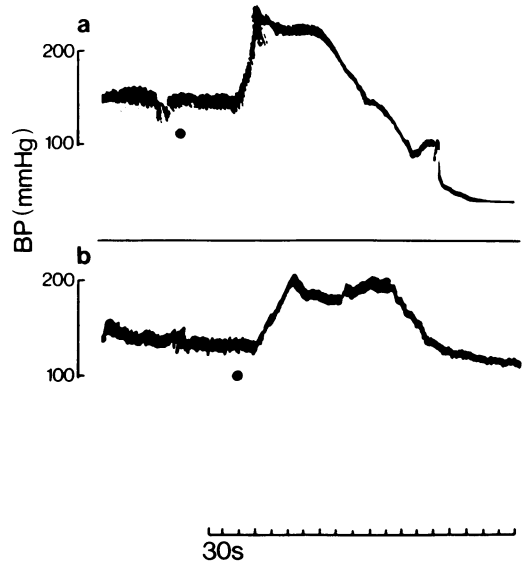

Figure 1 Records of arterial blood pressure obtained from 2 dogs (a and b) under chloralose anaesthesia. From the black dot, in (a) mepyramine maleate (10 mg/ml) and in (b) halopyramine (10 mg/ml) were continuously perfused from the lateral ventricle to the cisterna magna until the end of the experiment.

Results

Experiments with mepyramine and halopyramine

Perfusion of the cerebral ventricles, from the lateral ventricle to the cisterna magna, with a 10 mg/ml solution of either mepyramine or halopyramine resulted in a rise of arterial blood pressure followed by a fall. This is illustrated by the two experiments (a) and (b) of Figure 1. In (a) blood pressure began to rise about 2 min after the onset of perfusion with mepyramine, rose from about 150 mm to over 200 mmHg, remained elevated for less than 3 min and then fell to below 40 mmHg. In (b) blood pressure began to rise within 1 min of the onset of perfusion with halopyramine, rose from about 120 mm to about 200 mmHg, remained high for about 3 min and progressively declined although the perfusion with halopyramine continued (not included in the figure). In all the experiments, three with mepyramine and two with halopyramine, the

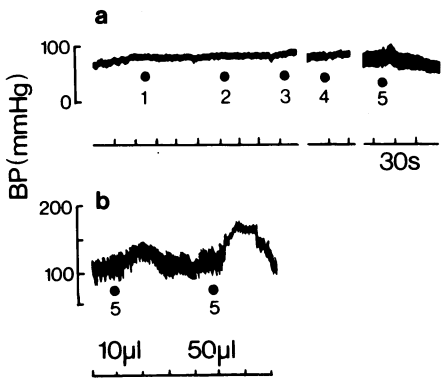

Figure 2 Records of arterial blood pressure obtained from 2 dogs (a and b) under chloralose anaesthesia with topical application of procaine to the floor of the fourth ventricle and adjoining areas. In (a) 2 μl of procaine (50 mg/ml) was applied to either side of medulla (1 and 3), 2-4 mm caudal to the obex (2), at the obex (4) and 2-4 mm rostral to it (5). In (b), 10 and 50 μl of procaine (50 mg/ml) were applied 2-4 mm rostral to the obex. This area is indicated in the inset of Figure 3.

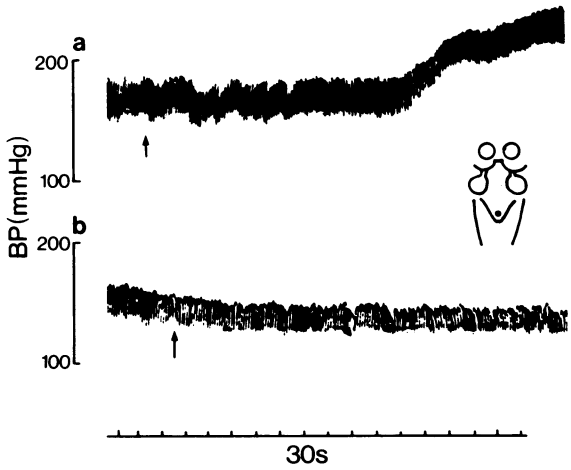

Figure 3 Record of arterial blood pressure obtained from a dog under chloralose anaesthesia. The lower record was obtained after cautery of an area on the floor of fourth ventricle a little rostral to the obex. The area is indicated in the inset. Arrows indicate start of procaine perfusion (20 mg/ml) at 0.1 ml/min from the lateral ventricle to the cisterna magna.

pressor response was followed by a fall below the preperfusion level.

Experiments with procaine

Site of action In four experiments 2 μl of a 50 mg/ml solution of procaine was applied to the sides of the medulla oblongata, or to the obex or to various other areas of the caudal half of the floor of the fourth ventricle. As shown in Figure 2 no blood pressure effects were obtained with this procedure except when the procaine was applied to an area 2 to 4 mm rostral to the obex. Then its application elicited a small rise in arterial blood pressure, and when this area was flooded with 10 or 50 μl of the procaine solution a strong pressor response ensued (Figure 2b). There was no area from which a depressor response was obtained on topical application of procaine to the rostral half of the floor of the fourth ventricle.

In eight experiments lesions of about 2 to 2.5 mm in diameter were made by cauterization in the area rostral to the obex which corresponded to the area from which procaine elicited a pressor response on topical application. After cauterization of this area perfusion of the cerebral ventricles with a 20 mg/ml solution of procaine no longer produced a pressor response in six, and produced a greatly diminished response in two experiments. The two records of Figure 3 illustrate one of the experiments in which the pressor response was abolished. Record (a) was obtained before cauterization; it shows the usual rise in arterial blood pressure which began within 6 min of the onset of the procaine perfusion. Record (b) was obtained after cauterization and the procaine perfusion no longer raised the arterial blood pressure. When similar lesions were made more rostrally, yet still within the caudal half of the floor of the fourth ventricle the pressor response persisted on subsequent perfusion of procaine through the cerebral ventricles. In one experiment in which the area postrema had been cauterized in an aseptic operation, perfusion of the cerebral ventricles with a 20 mg/ml procaine solution seven days later, produced the normal response followed by a fall in arterial blood pressure.

Carotid sinus denervation Bilateral denervation did not abolish the pressor response obtained when procaine was perfused in a 20 mg/ml solution through the cerebral ventricles. This result was obtained in six experiments, one of which is illustrated in Figure 4. Record (a) was obtained before denervation and shows the usual pressor responses to bilateral occlusion of the carotid arteries and the rise in blood pressure which began within 2 min of the onset of the procaine perfusion. Record (b) was obtained from the same dog after denervation. The success of the denervation was evident from the fact that the bilateral occlusion of the carotid arteries no longer produced pressor responses. Yet on perfusion of

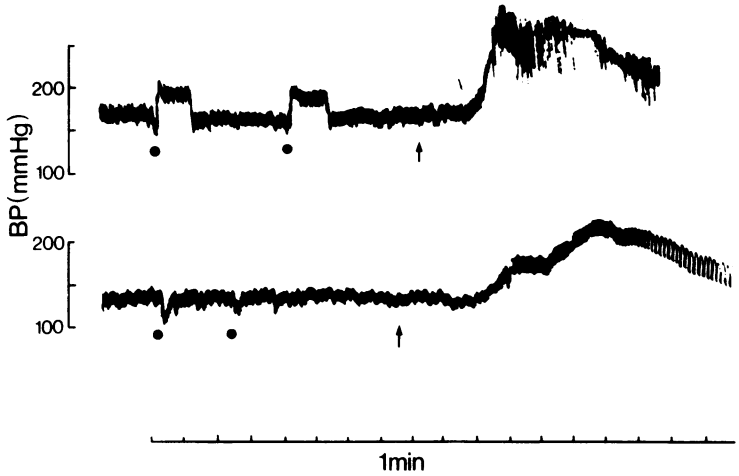

Figure 4 Record of arterial blood pressure obtained from a dog under chloralose anaesthesia. The lower tracing was taken after carotid denervation. At the black dots, bilateral carotid occlusion for 1 minute. At the arrows, perfusion of procaine (20 mg/ml) started from the lateral ventricle to the cisterna magna at 0.1 ml/minute.

the cerebral ventricles with procaine the blood pressure began to rise within 3 minutes.

Adrenalectomy In three dogs in which the perfusion of the cerebral ventricles with procaine (20 mg/ml) had produced strong pressor responses, the adrenal glands were removed on both sides. This itself lowered the blood pressure by 0 to 30 mmHg and in two it abolished the pressor reponse to perfusion of the cerebral ventricles in the procaine; in the third a much attenuated pressor response was obtained.

Hexamethonium and phentolamine In five experiments hexamethonium (4.5 to 6.3 mg/kg) was injected intravenously. This caused a fall in arterial blood pressure of 40 to 60 mmHg and abolished the pressor response to perfusion of procaine (20 mg/ml) through the cerebral ventricles. In two experiments phentolamine (6.7 and 10.8 mg/kg) was injected intravenously. This attenuated but did not abolish the pressor response to the perfusion with procaine.

Discussion

The present experiments support the view that procaine, cinchocaine and lidocaine have pressor actions when injected into the cerebral ventricles because they are local anaesthetics. Other substances that have local anaesthetic properties should therefore have similar actions, even if they have other pharmacological properties for which they are used. Propranolol, for instance is used clinically for its β-adrenoceptor blocking action, but in addition it has local anaesthetic properties and it was found to produce a pressor effect when injected into the cerebral ventricles (Shrivastava *et al.*, 1973; Dollery *et al.*, 1973). Mepyramine and halopyramine are antihistamines, which have relatively strong local anaesthetic properties as well, and in the present experiments they were shown to produce a rise in arterial blood pressure when perfused through the cerebral ventricles.

It was previously concluded that the pressor response to procaine perfused through the cerebral ventricles was due to an action on structures situated in the caudal part of the floor of the fourth ventricle, since it was obtained when the other parts of the ventricular system were excluded from the perfusion with procaine. This conclusion is supported by the results of the present experiments in which the procaine was applied topically to the floor of the fourth ventricle or perfused through the cerebral ventricles after having made lesions to the floor of this ventricle. With these methods the site where procaine acts when producing its pressor effect could be pinpointed to a 5 mm^2 area in the caudal half of the floor of the fourth ventricle 2 to 4 mm rostral to the obex. This area corresponds to the well known depressor or vasodilator area from which a fall in arterial blood pressure is obtained on electrical stimulation (Alexander, 1946; Lindgren & Uvnas, 1954) and which is also stimulated by nicotine (Guertzenstein, 1971). It

can therefore be concluded that procaine produces a rise in arterial blood pressure because it removes the inhibitory tone exerted from this area.

It has always been assumed that the inhibitory tone from this area is mediated through the sympathetic nervous system. Results of the present experiments support this view as the pressor response to procaine was abolished or attenuated by procedures which interfere with the sympathetic discharge, i.e. removal of the adrenal glands, intravenous hexamethonium and phentolamine. The relative importance of increased adrenaline discharge from the adrenal glands and of increased vasoconstrictor tone in the pressor response to procaine seems to vary, because in three experiments the pressor response was abolished twice and attenuated once by removal of the adrenal glands.

The present experiments do not deal with the late depressor effect following the initial pressor effect on perfusion of cerebral ventricles with procaine. The depressor response to application of procaine to cerebral ventricles in anaesthetized dogs was described by Loeschcke & Koepchen (1958). Mitchell, Loeschcke, Massion & Severinghaus (1963) and Severinghaus, Mitchell, Richardson & Singer (1963) suggest a chemoreceptor area in the ventral surface of the brain stem as the site of action of this depressor effect. Haranath & Venkatakrishna-Bhatt (1958a) observed only a fall in blood pressure when procaine was injected into the subarachnoid space around the brain stem through an open cisterna, while at the same time its access to the fourth ventricle was prevented by a simultaneous perfusion from the lateral ventricle with artifical c.s.f. at twice the speed.

References

ALEXANDER, R.S. (1946). Tonic and reflex functions of the medullary sympathetic cardiovascular centres. *J. Neurophysiol.*, **9**, 205-217.

BHATTACHARYA, B.K. & FELDBERG, W. (1958). Perfusion of cerebral ventricles: effects of drugs on outflow from cisterna and aqueduct. *Br. J. Pharmac. Chemother.*, **13**, 156-162.

BORISON, H.L., HARANATH, P.S.R.K. & McCARTHY, L.E. (1972). Respiratory responses to chemical pulses in the cerebrospinal fluid of cats. *Br. J. Pharmac.*, **44**, 605-616.

DAY, M.D. & ROACH, A.G. (1974). Central α- and β-adrenoceptors modifying arterial blood pressure and heart rate in conscious cats. *Br. J. Pharmac.*, **51**, 325-34.

DOLLERY, C.T., LEWIS, P.J., MEYERS, M.G. & REID, J.L. (1973). Central hypotensive effect of propranolol in the rabbit. *Br. J. Pharmac.*, **48**, 343P.

GUERTZENSTEIN, P.G. (1971). Stimulation by nicotine of a vasodilator area on the floor of the fourth ventricle. *J. Physiol.*, **214**, 5-6P.

HARANATH, P.S.R.K., NASEEM AYESHA-BEGUM & SITARAMAYYA, G.V. (1965). The effects of procaine injected into cerebral ventricles of conscious and anaesthetized dogs. *Br. J. Pharmac.*, **24**, 339-347.

HARANATH, P.S.R.K. & VENKATAKRISHNA-BHATT, H. (1968a). Procaine perfused into cerebral ventricles and subarachnoid space in conscious and anaesthetized dogs. *Br. J. Pharmac.*, **34**, 408-416.

HARANATH, P.S.R.K. & VENKATARISHNA-BHATT, H. (1968b). Studies on cinchocaine and lidocaine adminstered into cerebral ventricles of conscious and anaesthetized dogs. *Ind. J. Med. Res.*, **56**, 217-226.

LINDGREN, P. & UVNAS, B. (1954). Postulated vasodilator center in the medulla oblongata. *Am. J. Physiol.*, **176**, 68-76.

LOESCHCKE, H.H. & KOEPCHEN, H.P. (1958). Beeinflussung von Atmung und Vasomotorik durch Einbringen von Novocain in die Liquorraume. *Pflugers Arch. ges. Physiol.*, **266**, 611-627.

MITCHELL, R.A., LOESCHCKE, H.H., MASSION, W.H. & SEVERNGHAUS, J.W. (1963). Respiratory responses mediated through superficial chemosensitive areas on the medulla. *J. appl. Physiol.*, **18**, 523-533.

SEVERINGHAUS, J.W., MITCHELL, R.A., RICHARDSON, B.W. & SINGER, M.M. (1963). Respiratory control at high altitude suggesting active transport regulation of CSF pH. *J. appl. Physiol.*, **18**, 1155-1166.

SHRIVASTAVA, R.K., KULSHRESTHA, V.K., SINGH, N. & BHARGAVA, K.P. (1973). Central cardiovascular effects of intracerebroventricular propranolol. *Eur. J. Pharmac.*, **21**, 222-229.

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