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BLOOD PRESSURE EFFECTS OBTAINED BY DRUGS APPLIED TO THE VENTRAL SURFACE OF THE BRAIN STEM

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SUMMARY

1. In cats anaesthetized with pentobarbitone sodium the effect on arterial blood pressure was examined of substances applied bilaterally to the exposed ventral surface of the brain stem by means of Perspex rings placed lateral to the pyramids and caudal to the trapezoid bodies. Routinely, atropine methyl nitrate, which does not pass the blood–brain barrier, was injected I.V.

2. The cholinomimetic substances carbachol and physostigmine, and the amino acids glycine and GABA, caused a fall in arterial blood pressure.

3. Atropine produced a small but definite rise in arterial blood pressure, antagonized the depressor effects of the cholinomimetic substances, but not those of the amino acids.

4. Strychnine, leptazol and tubocurarine, caused a rise in arterial blood pressure.

5. The depressor and pressor effects are due to changes in vasomotor tone. They are central effects brought about by penetration of the substances into the brain tissue from the ventral surface of the brain stem. They are not due to their absorption into the blood stream.

6. The depressor effects of the cholinomimetic substances may imitate the action of cholinergic neurones, and those of the amino acids that of central inhibitory neurones ending on cells near the ventral surface of the brain stem and exerting an inhibitory influence on vasomotor tone. The pressor effects of strychnine and tubocurarine may in part result from 'disinhibition', i.e. from an antagonistic action produced by these drugs on the amino acids released from the central inhibitory neurones.

INTRODUCTION

Recently it was found that a few milligrams of pentobarbitone sodium injected into the cerebral ventricles of anaesthetized cats lowered arterial

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blood pressure, and that the effect was due to an action on structures situated near the ventral surface of the brain stem and reached by the pentobarbitone sodium after it had passed through the lateral recesses into the subarachnoid space. When applying the pentobarbitone sodium by means of Perspex rings to various parts of the exposed ventral surface of the medulla, it was found to act on a region situated caudal to the trapezoid bodies and lateral to the pyramids. To be effective the pentobarbitone sodium had to be applied bilaterally to this region (Feldberg & Guertzenstein, 1972). Within the area covered by each Perspex ring, Petrovický (1968) had found a region in which groups of nerve cells lie immediately under the pia mater within the marginal glia. The nerve cells belong to the nucleus paragiganto cellularis.

The method of applying pentobarbitone sodium bilaterally to this region by means of Perspex rings has now been used for a number of other drugs. The present paper deals with the blood pressure effects obtained from this region with two cholinomimetic substances carbachol and physostigmine, with their antagonist atropine, with the two amino acids glycine and γ-aminobutyric acid (GABA) which are considered to be transmitter substances of central inhibitory neurones, and with strychnine, tubocurarine and leptazol. Strychnine and tubocurarine are considered to be for the inhibitory central neurones what atropine is for cholinergic neurones, and are also considered to be antagonists of acetylcholine at certain central cholinergic synapses (for references see Curtis, 1969; Phillis & York, 1967, 1968). Some of the results have been communicated to the Physiological Society (Guertzenstein, 1972).

METHODS

The experiments were done on cats weighing between 3·6 and 5·2 kg. The cats were anaesthetized by I.P. injection of pentobarbitone sodium (36 mg/kg), supplemented whenever required later in the experiment by an I.V. injection of 12 or 18 mg pentobarbitone sodium. The methods for cannulating the trachea, recording arterial blood pressure from the left femoral artery, exposing the ventral surface of the brain stem and putting the drugs on to this surface by means of two Perspex rings, were described previously (Feldberg & Guertzenstein, 1972). A diagram of the Perspex rings with their holder is given in Fig. 1. The inset is a diagram of the ventral surface of the cat's brain stem and indicates the regions covered by the rings. They were not round as in the previous experiments, but slightly oval. Their inner diameters were 5 and 4 mm with the long axes lying in one line.

The drugs were placed inside each ring in a volume of 10 or 20 μl. through openings on opposite sides of the holder with the help of a fine polyethylene tube attached to the hypodermic needle of the syringe. The filling of one ring is indicated in the diagram.

To place the Perspex rings on to the ventral surface of the brain stem, the head of the anaesthetized cat, lying on its back, was fixed to the ear bars and mouthpiece of a Dell-Moruzzi stereotaxic instrument. The skin over the neck was opened in the

mid line, the trachea cannulated close to the thorax and the larynx was cut between ligatures, one being placed as near to the pharynx as possible, the other close to the tracheal cannula. The larynx was then retracted and fixed to the head holder. The basal plate of the occipital bone was freed from its muscles and removed with nibbling forceps as close to the bullae tympany as possible without injuring the nerves passing through the jugular foramina. A small hole was then made into the exposed dura about a millimetre lateral to the mid line to avoid injury of the underlying basilar artery. A blunt spatula was inserted into the hole, the dura was carefully lifted and opened with a pair of fine scissors in the mid line along the exposed length of the dura. Through this longitudinal slit, the Perspex rings were slipped under the dura, the holder being placed so that the Perspex rings were one in front of the other. The holder was then rotated 90° so that the Perspex rings came to lie side by side under the dura with their edges gently wedged under the bone.

In most experiments the cats were artificially ventilated through the tracheal cannula and atropine methyl nitrate (2 mg/kg) was injected I.V. The methyl nitrate was used because it does not pass the blood–brain barrier and therefore would not interfere with any action of the drugs on the ventral surface of the brain stem. It was given not only when the effects of topical application of cholinomimetic substances were investigated to rule out possible effects due to absorption but also to prevent cardiac slowing which might be produced by vagal excitation. Naturally, the atropine would also prevent any vasodilatation which might be produced by excitation of sympathetic cholinergic vasodilator fibres.

Materials. The following compounds were used: atropine methyl nitrate (Sigma); atropine sulphate (British Drug Houses); carbachol (Savoury & Moore); GABA (Light); glycine (British Drug Houses); leptazol (Martindale); physostigmine sulphate (British Drug Houses); strychnine hydrochloride (Hopkins & Williams); D-tubocurarine chloride (Burroughs Wellcome & Co.).

For the topical application to the ventral surface of the brain stem, the substances were dissolved in artificial c.s.f. which had a pH of 8·7. The pH was lowered by the addition of the drugs, but not below neutral except in the case of physostigmine which in a concentration of 100 mg/ml. lowered the pH to 6·5. However, the blood pressure effects observed were not due to the pH of the solutions because when either artificial c.s.f. or artificial c.s.f. acidified to pH 6·5 was placed inside the Perspex rings blood pressure did not change. The solutions used for intravenous injections were made up in 0·9 % NaCl. The doses of the compounds used as salts refer to the salt.

RESULTS

Carbachol. Applied to the ventral surface of the brain stem in concentrations of between 2 and 6 mg/ml. carbachol caused a fall in arterial blood pressure. Since 10 μl. were placed inside each ring the carbachol present in both rings amounted to between 40 and 120 μg. Results obtained on three cats are shown in Fig. 2. After filling the rings with the carbachol solution, blood pressure began to fall within 2–3 min and fell 60–80 mm Hg. When the carbachol was washed out from the rings 10 min later, blood pressure remained low for nearly an hour, and it took another 40 min for full recovery. This is illustrated in the top record.

The fall was not due to absorption, because if all the carbachol placed in the rings had been absorbed it would not have lowered blood pressure. For

instance, intravenous infusion of 60–100 μg carbachol over 10 min did not affect blood pressure in cats treated with I.V. atropine methyl nitrate. Even when given in a single I.V. injection, blood pressure did not fall. This is shown at the beginning of the top record by the arrow which indicates an intravenous injection of 60 μg carbachol.

There was an indication that the fall produced by topical application of carbachol depended to some extent on the blood pressure level existing before its application. When applied in a concentration of 6 mg/ml., the

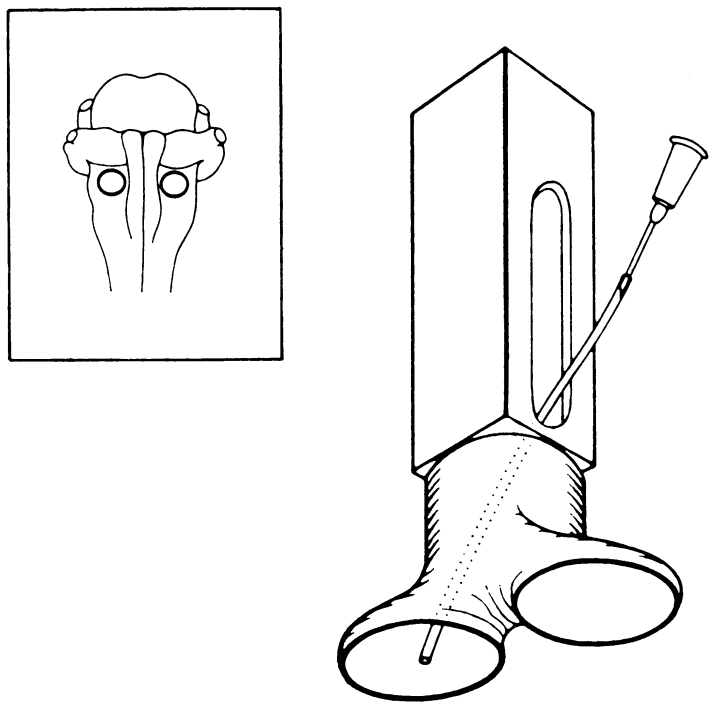

Fig. 1. Diagram of the Perspex rings with holder used to apply drugs to the ventral surface of the cat's brain stem. Inset: diagram of the ventral surface of the brain stem; the ovals indicate the areas to be covered by the Perspex rings.

fall amounted to between 50 and 60 mm Hg in four cats with an initial pressure (diastolic) of between 105 and 110 mm Hg, and to 75, 80 and 95 mm Hg in three cats in which the initial pressure was 125, 150 and 180 mm Hg respectively. The eighth cat did not follow this pattern; the fall amounted to only 15 mm Hg although the initial blood pressure was 125 mm Hg.

In the experiments of Fig. 2 the cats were not artificially ventilated and

the topical application of carbachol resulted in pronounced tachypnoea which began before the blood pressure started to fall. The possibility that this effect was due to absorption was not excluded as tachypnoea was obtained also with I.V. injections of carbachol.

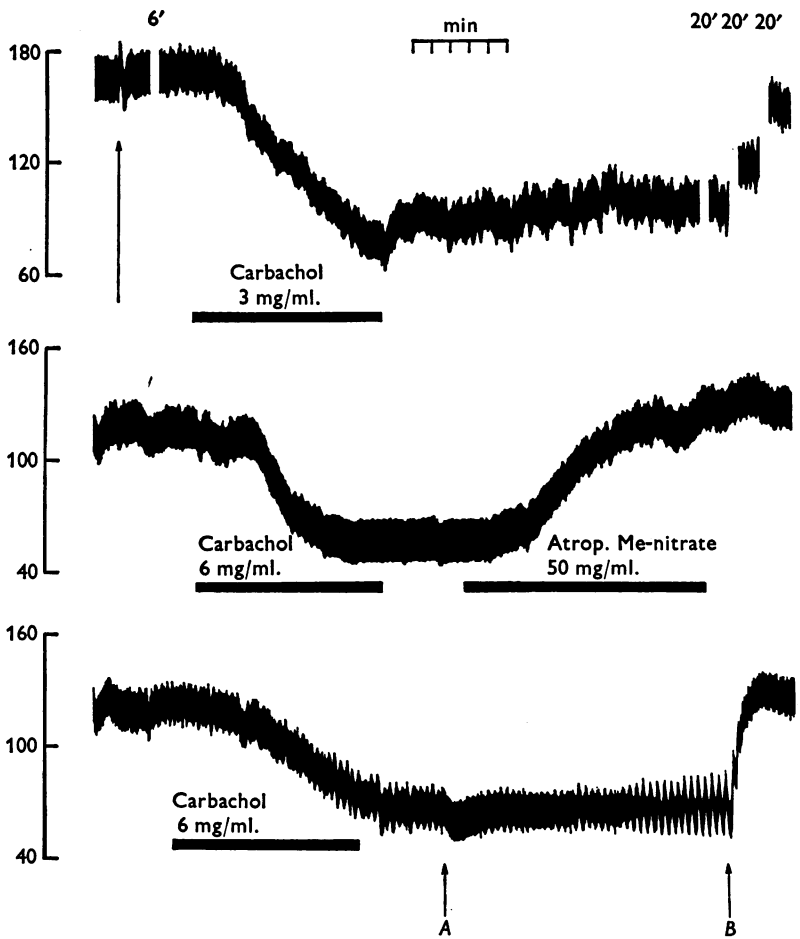

Fig. 2. Records of arterial blood pressure from three cats weighing between 4·2 and 4·4 kg anaesthetized with I.P. pentobarbitone sodium. Atropine methyl nitrate injected I.V. The black horizontal bars under each record indicate periods of topical application of carbachol or atropine methyl nitrate in the concentrations given above the bars. The volume of the solutions placed inside each ring was 10 μl. The arrow under the top record indicates intravenous injection of 60 μg carbachol. The breaks in the record represent intervals of 6 and 20 min as indicated. The arrows in the bottom record indicate I.V. injection, at *A*, of 1 mg atropine methyl nitrate, and, at *B*, of 1 mg atropine sulphate. Arterial blood pressure in mm Hg. Time in min.

Physostigmine. Applied to the ventral surface of the brain stem in concentrations between 12·5 and 100 mg/ml., physostigmine produced a steep fall in blood pressure. A particularly strong effect obtained with 25 mg/ml. applied for 4·5 min is illustrated in the top record of Fig. 3. Blood pressure began to fall during the first minute of application and had fallen by about 100 mm before the physostigmine was washed out. Recovery began after about 20 min, i.e. earlier than in the corresponding experiments with carbachol.

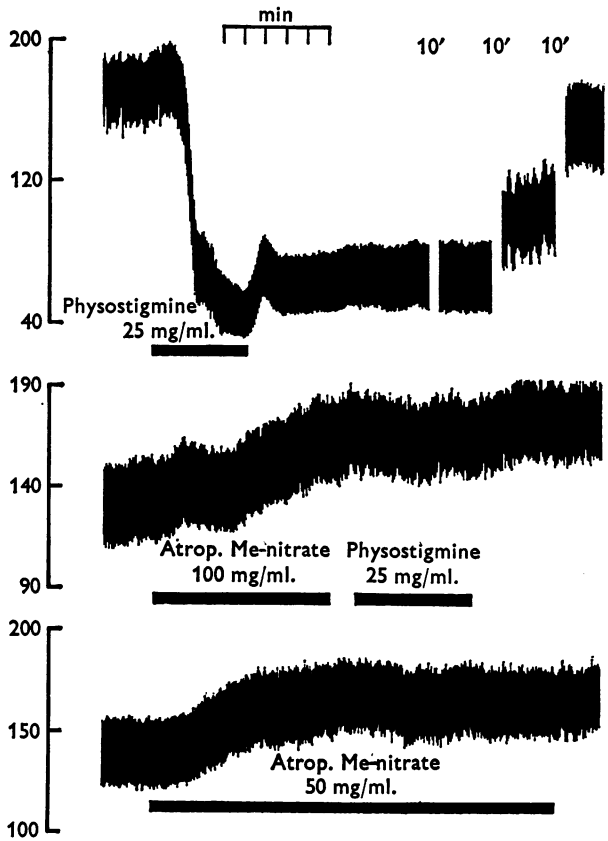

Fig. 3. Records of arterial blood pressure from two cats anaesthetized with I.P. pentobarbitone sodium and artificially ventilated. Atropine methyl nitrate injected I.V. Top and middle record from the same cat weighing 3·6 kg. Middle record direct continuation of top record. Bottom record from a cat weighing 4·2 kg. The black horizontal bars under each record indicate periods of topical application of solutions of physostigmine or atropine methyl nitrate in the concentrations given above the bars. The volume of the solutions placed inside each ring was 20 μl. Breaks in the top record indicate intervals of 10 min. Arterial blood pressure in mm Hg. Time in min.

There was great variability in the depressor effect, independent of the initial arterial blood pressure. Physostigmine was applied in a concentration of 12·5 mg/ml. in only one experiment; with this concentration the fall produced was 10 mm Hg. In four experiments, including the one illustrated by the top record of Fig. 3 the physostigmine was applied in a concentration of 25 mg/ml. and the resulting fall varied between 20 and 100 mm Hg (mean 48 mm Hg). In ten experiments in which it was applied in a concentration of 50 mg/ml. the fall varied between 30 and 110 mm Hg (mean 55 mm Hg), and in three in which it was applied in a concentration of 100 mg/ml. the fall varied between 40 and 60 mm Hg.

Again the fall was not the result of absorption, because an I.V. injection of 1 mg physostigmine (the amount placed in both rings of the experiment illustrated in the top record of Fig. 3) produced either no fall or only a transient small fall in the blood pressure.

In a few experiments without artificial ventilation the topical application of physostigmine resulted in respiratory effects which varied with the concentrations used. With 12·5–25 mg/ml. pronounced tachypnoea was the sole respiratory effect, with higher concentration (50–100 mg/ml.) tachypnoea was followed by respiratory depression leading to respiratory arrest. These respiratory effects occurred without muscular fasciculation which dominated the picture when physostigmine, in the same amounts as placed in the Perspex rings, was injected I.V. Therefore, the respiratory effects produced on local application were unlikely to have been produced after absorption of the physostigmine into the blood stream.

Glycine and GABA. These two amino acids lowered arterial blood pressure when applied to the ventral surface of the brain stem. The effects were shorter-lasting than those of carbachol or physostigmine. When the effects of the two amino acids were compared in the same cat glycine was found to be more active. This is illustrated in Fig. 4. The four records were obtained from the same cat. The depressor effect of 50 mg/ml. glycine was stronger than that of GABA 100 mg/ml., and that of glycine 25 mg/ml. was about the same as that of GABA 50 mg/ml. Since the molecular weight of glycine is 75, that of GABA 103, the potency of glycine is not quite twice that of GABA. The depressor effects were not due to absorption of the amino acids into the bloodstream because the amounts placed inside the rings did not lower blood pressure when injected I.V.

On topical application in a concentration of either 50 or 100 mg/ml. the depressor effect of glycine varied normally between 25 and 45 mm Hg (seven experiments) but in one experiment with 100 mg/ml. the fall was 100 mm Hg.

Atropine. Applied in a concentration of 50 or 100 mg/ml. to the ventral surface of the brain stem, atropine methyl nitrate produced a small but

definite rise in arterial blood pressure. This is illustrated in the middle and bottom records of Fig. 3. The rise was maintained as long as the atropine was kept in the Perspex rings and at least for another hour, the maximal time of observation, after the atropine was washed out. In addition, the atropine antagonized the depressor effects of carbachol and physostigmine similarly applied but not the depressor effect of topically applied glycine.

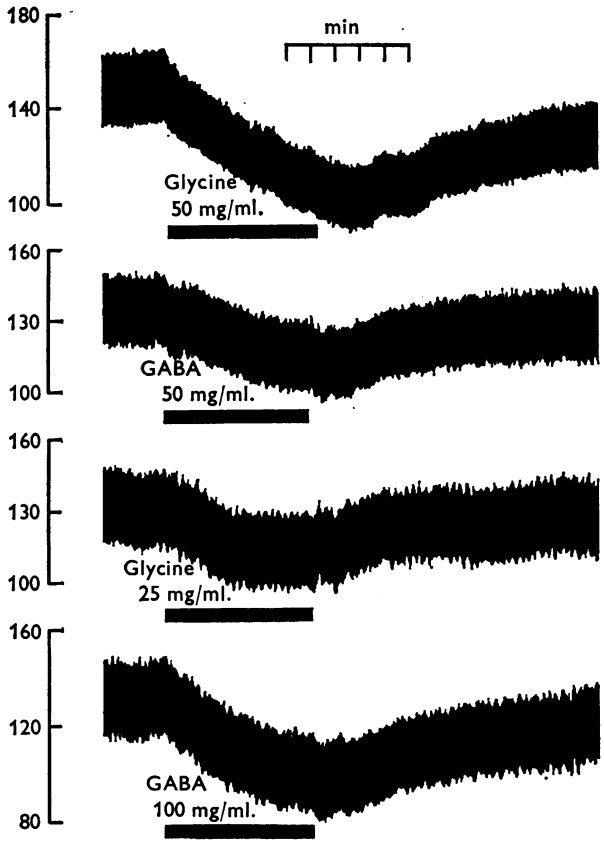

Fig. 4. Records of arterial blood pressure from a 4·3 kg cat anaesthetized with I.P. pentobarbitone sodium and artificially ventilated. Atropine methyl nitrate injected I.V. The black horizontal bars indicate periods of topical application of solutions of glycine and GABA in the concentrations given above the bars. The volume of solutions placed inside each ring was 20 μl. About 20 min interval between each record. Arterial blood pressure in mm Hg. Time in min.

When the atropine was applied before the cholinomimetic substances it prevented their depressor effects, and when applied afterwards, during the fall, the blood pressure recovered rapidly. The middle record of Fig. 3

shows the prevention of the depressor effect of physostigmine when its topical application followed that of atropine, and the middle record of Fig. 2 shows the rapid recovery of the blood pressure when atropine methyl nitrate was applied 4 min after carbachol had been washed out

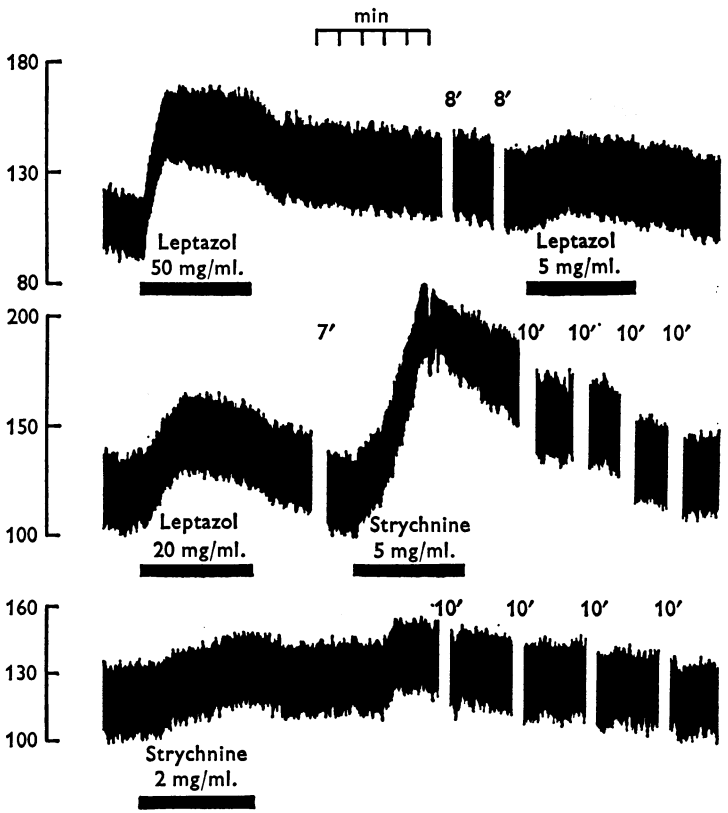

Fig. 5. Records of arterial blood pressure from a 4·0 kg cat anaesthetized with I.P. pentobarbitone sodium and artificially ventilated. Atropine methyl nitrate injected I.V. No interval between top, middle and bottom record. The black horizontal bars indicate periods of topical application of solutions of leptazol or strychnine in the concentrations given above the bars. The volume of solutions placed inside each ring was 20 μl. The breaks in the records represent intervals of 7, 8 and 10 min as indicated. Arterial blood pressure in mm Hg. Time in min.

of the Perspex rings. Without the application of atropine the blood pressure would have remained low for about another hour, as in the experiment of the top record of Fig. 2.

The rapid recovery of the blood pressure on topical application of atropine methyl nitrate was not due to its absorption. This is evident from the

result shown in the bottom record of Fig. 2. The arrow *A* indicates an I.V. injection of 1 mg of atropine methyl nitrate. This is the amount which was placed inside both rings in the experiment of the middle record of the Figure. The blood pressure did not recover. However, when, 15 min later, 1 mg of the sulphate of atropine, which passes the blood–brain barrier, was injected instead, the result was different. The arrow *B* indicates its I.V. injection. Recovery was immediate and blood pressure rose steeply.

Strychnine and leptazol. Both substances raised arterial blood pressure when acting from the ventral surface of the brain stem, but strychnine was more potent than leptazol and its effect was longer lasting. To obtain a rise of between 30 and 40 mm Hg it was necessary to apply strychnine in a concentration of 5–20 mg/ml. and leptazol in a concentration of 25–50 mg/ml. The results illustrated in Fig. 5 were from a particularly sensitive cat and the topical application of strychnine or leptazol was each time for 5 min. With 5 mg strychnine/ml., blood pressure rose about 80 mm, the maximum was reached before the strychnine was washed out, and it took more than 45 min for the rise to subside. With 2 mg strychnine/ml. which was about the threshold concentration, the rise amounted to 15 mm Hg only, yet the effect lasted as long as with the stronger concentration. With 1 mg/ml. no change in blood pressure was obtained (not shown in the Figure). With leptazol the threshold concentration was about 5 mg/ml. which produced a rise of about 10 mm Hg; the effect lasted only a few minutes. With 20 mg leptazol/ml. the rise amounted to about 25 mm Hg, and with 50 mg/ml. to about 40 mm Hg, and with both concentrations the effect was of shorter duration than with strychnine. The records show that the rise produced by 2 mg strychnine/ml. is smaller than that produced by 20 mg leptazol/ml., but that the rise produced by 5 mg strychnine/ml. is greater than that produced by 50 mg leptazol/ml. This implies that the dose–response curve for strychnine is stronger than for leptazol.

Strychnine exerted its pressor effect also when applied during the fall in blood pressure produced by the topical application of either glycine or carbachol.

The pressor effects of both strychnine and leptazol were not due to absorption because when injected I.V. in the amounts placed inside the rings, leptazol did not affect blood pressure and strychnine produced a fall.

Tubocurarine. Applied topically for 5 min to the ventral surface of the brain stem in a concentration of 5 or 10 mg/ml. tubocurarine caused a rise in arterial blood pressure of between 25 and 40 mm Hg. The rise differed from that produced by either strychnine or leptazol in that it developed and subsided more gradually. The maximum rise was not reached until 20 min after the tubocurarine was washed out, and it then took between

2 and 3·5 hr for the rise to subside. Again absorption was excluded because the amounts placed inside the rings did not affect blood pressure, or produced only a small fall when injected intravenously.

DISCUSSION

The depressor and pressor effects obtained with the various substances applied by means of Perspex rings to the exposed ventral surface of the brain stem are due to changes in sympathetic vasomotor tone. They are central effects produced by an action on structures near the ventral surface of the brain stem and occur as the substances penetrate the brain in the regions covered by the fluid in the Perspex rings. Absorption into the blood stream could be excluded as the cause because for each substance it was shown that when the total amount placed inside the rings was injected I.V. either blood pressure was not affected, or the effect was much weaker than on topical application, or the injection produced the opposite effect. Yet only part of the substances placed inside the rings could have been absorbed during the short period of topical application.

As the depressor and pressor effects were obtained within a few minutes of topical application, penetration of the brain stem can have occurred to a short distance only. Fewer observations have been made with regard to penetration from the pia mater than from the ependyma. In anaesthetized cats penetration was studied for bromophenol blue applied topically to the dorsal surface of the cervical spinal cord (Feldberg & Fleischhauer, 1960), and for labelled potassium applied by perfusion to both outer and inner surfaces of the cerebrum (Pape & Katzman, 1972). Penetration of the potassium was slower from the subarachnoid space across the pia mater than from the ventricular cavity across the ependyma. From these findings with bromophenol blue and potassium it would appear unlikely that the substances placed inside the Perspex rings could reach, within a few minutes, structures situated more than 1 or 1·5 mm away from the ventral surface of the brain stem. In this connexion it is worth mentioning that with pentobarbitone sodium a depressor action was obtained also when introduced by micro-injections into the brain stem, but then only when the injections were made not more than 1 mm away from the ventral surface (Feldberg & Guertzenstein, 1972).

Pentobarbitone sodium, being an anaesthetic, might act on nerve fibres and not on nerve cells when producing its vasodepressor effect. Such an action would be difficult to postulate for the depressor and pressor effects obtained with the substances used in the present experiments as they are all associated with an action on synapses and nerve cells and not with an action on nerve fibres. The different drugs used may act, however, on different synapses and, since the area under each Perspex ring is relatively

large, the cell groups affected by these drugs may not all belong to the same nucleus.

Three findings provide suggestive evidence for the presence of cholinergic neurones innervating cells situated close to the ventral surface of the brain stem, the two depressor effects obtained with carbachol and physostigmine, and the pressor effect obtained with atropine. Cells innervated by cholinergic neurones are cholinoceptive. Therefore, they respond to carbachol which imitates the action of acetylcholine. Further, physostigmine which inhibits the enzymic destruction of acetylcholine released from the cholinergic neurones, would act like carbachol and lower blood pressure. Finally, the finding that atropine not only reversed the depressor effect of the two cholinomimetic substances, but by itself produced a small but definite rise, suggests that a continuous activity and release of acetylcholine is going on in these neurones, and that this activity exerts an inhibitory influence on vasomotor tone which is removed by atropine.

Previously, Armitage & Hall (1967) described a central vasodepressor action for carbachol on its injection into the cerebral ventricles of anaesthetized cats. They concluded that the site of its action was 'the ventral brain stem'. Most likely the site was the same as that where carbachol acted in the present experiments.

The action of the cholinomimetic substances on the cholinoceptive cells may be an inhibitory or an excitatory response. The effects can be classified as muscarinic because they were abolished by atropine. From the experiments of Bradley, Dhawan & Wolstencroft (1966) with iontophoretic application of acetylcholine to brain stem neurones, we know that both excitatory and inhibitory responses to acetylcholine are antagonized by atropine, but that dihydro-β-erythroidine antagonizes only the excitatory responses. If the same situation were to pertain for the depressor responses obtained with the cholinomimetic substances, the problem may be solved by finding out whether dihydro-β-erythroidine antagonizes these depressor responses or not.

The depressor effects obtained with glycine and GABA may imitate effects of central inhibitory neurones ending near the ventral surface of the brain stem. If so, these neurones influence vasomotor tone in the same way as the cholinergic neurones, and the two types of neurones would either innervate the same cells, but act on different receptors, or innervate different cells which need not even belong to the same nucleus.

With GABA a fall in arterial blood pressure was previously obtained on its injection into the vertebral artery of anaesthetized cats (Robbin & Guth, 1970). The action may have been on the same synapses on which GABA acted in the present experiments.

Strychnine, leptazol and tubocurarine had the opposite effect from the amino acids when applied to the ventral surface of the brain stem. They caused a rise in blood pressure due to increased vasomotor tone. These effects may not be fully accounted for by a direct excitatory action on nerve cells, but may result at least in part from 'dis-inhibition', that is from an antagonistic action produced by these drugs on the amino acids released from central inhibitory neurones. The same problem exists for the localized spike discharge which is produced in the cerebral cortex of cats when these drugs are introduced by micro-injection into the grey matter (Banerjee, Feldberg & Georgiev, 1970).

With tubocurarine central pressor effects have previously been described by Feldberg & Fleischhauer (1962). A pressor effect was obtained in anaesthetized cats on injection of tubocurarine into the cerebral ventricles and into the cisterna magna as well as on perfusion of tubocurarine from lateral ventricles to either cisterna or aqueduct. Two sites of action were postulated, one reached from the ventricles, and the other reached from the subarachnoid space. This latter site may be situated near the ventral surface of the brain stem and be the same from where the pressor effect of tubocurarine was obtained in the present experiments.

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