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BLOOD PRESSURE EFFECTS OF LEPTAZOL APPLIED TO THE VENTRAL SURFACE OF THE BRAIN STEM OF CATS

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SUMMARY

1. In anaesthetized cats leptazol (200 mg/ml) and sodium pentobarbitone (30 mg/ml) were applied topically to an area of the exposed ventral surface of the medulla oblongata, which lies between the rootlets of the twelfth cranial and first cervical nerve. The drugs were applied either bilaterally by means of paired Perspex rings or unilaterally by means of a single Perspex ring. Their effects on arterial blood pressure, heart rate and respiration were examined during two stages of anaesthesia, during 'surgical anaesthesia' produced by an intravenous injection of chloralose at 60 mg/kg, and during deeper anaesthesia attained by two additional intravenous injections of chloralose at 30 mg/kg.

2. Both the bilateral and unilateral application of leptazol produced a fall in arterial blood pressure during surgical anaesthesia, but a rise during deepened anaesthesia. After a preceding topical application of sodium pentobarbitone the fall became attenuated or abolished, whereas the rise became potentiated.

3. Sodium pentobarbitone itself affected blood pressure as well as respiration when applied bilaterally. It then produced pronounced tachypnoea independent of the depth of anaesthesia and a fall in arterial blood pressure during deepened anaesthesia. Its unilateral application did not affect respiration, nor did it affect usually arterial blood pressure, although during deepened anaesthesia it occasionally produced a fall in blood pressure.

4. The area from which the pressor response to leptazol was obtained lay 7–11 mm caudal to the lower border of the trapezoid bodies, i.e. about 2 mm more caudally than the 'nicotine-sensitive area' from which a depressor response to leptazol is evoked. Thus the two areas, though not identical, overlap.

5. The result obtained with sodium pentobarbitone suggest that the area for the pressor response to leptazol (a) plays a role in maintaining vasomotor tone during deepened anaesthesia and (b) exerts a strong inhibitory effect on the respiratory rate during both surgical and deepened anaesthesia.

INTRODUCTION

In anaesthetized cats leptazol applied to the cranial portion of the exposed ventral surface of the medulla oblongata, referred to also as the 'glycine-sensitive area', produces a rise in arterial blood pressure. However, different statements have

appeared in the literature concerning the blood pressure effects produced by leptazol when applied to a more caudal portion of this surface. A pressor response was observed in experiments which dealt with vasopressin release evoked by various drugs, including leptazol, when applied in this way (Feldberg & Rocha e Silva, 1978), but in an extensive analysis of the cardiovascular effects of leptazol a fall was obtained when the leptazol was applied to an area which lies 3–6 mm lateral from the mid line and 5–9 mm caudal to the lower border of the trapezoid bodies, an area also termed the 'nicotine-sensitive area' (Guertzenstein & Lopes, 1984).

Both effects could be reproduced in the present experiments and two factors were found to determine whether leptazol would produce a fall or a rise in blood pressure. They were (1) the exact localization on the ventral surface where leptazol was applied and (2) the depth of chloralose anaesthesia.

The experiments to be described deal mostly with the pressor response to leptazol, the depressor effect having been investigated more thoroughly in a previous study (Guertzenstein & Lopes, 1984). In addition, the effect of topical application of sodium pentobarbitone, thought to result from an inhibitory action, was examined to find out how it would affect blood pressure and respiration when applied to the area from where the pressor response to leptazol is evoked.

METHODS

Cats of either sex weighing 2·4–4·2 kg were anaesthetized with an intravenous injection of a 1 % chloralose solution to produce one of the following two stages of anaesthesia, to be referred to in the text as 'surgical anaesthesia' and as 'deepened anaesthesia'. To produce surgical anaesthesia chloralose at 600 mg/kg was injected into a cephalic foreleg vein; to produce deepened anaesthesia the initial injection was followed by two additional injections of chloralose at 30 mg/kg into the right saphenous vein cannulated during the surgical anaesthesia induced by the first injection. The interval between each of the chloralose injections was at least 30 min.

Arterial blood pressure was recorded from a cannula inserted into the right femoral artery by means of a transducer, connected through a Cambridge pre-amplifier (type 72342) to a Smith's Servoscribe potentiometer pen recorder. Heart rate was counted with a digital counter connected to the pen recorder. The trachea was cannulated and respiratory movements were recorded with a thermistor probe inserted into the trachea and connected to the pen recorder. In a few experiments artificial ventilation was applied using a (Palmer Ideal) respiratory pump.

To expose the ventral surface of the medulla oblongata the anaesthetized cat was placed in the supine position and its head was fixed to the ear bars and mouthpiece of a stereotaxic instrument. The method of exposing the ventral surface and of applying drugs to it, either bilaterally by means of paired Perspex rings or unilaterally by means of a single Perspex ring, attached to a holder, has been described previously (Feldberg & Guertzenstein, 1972, 1976; Guertzenstein, 1973; Bisset, Feldberg, Guertzenstein & Rocha e Silva, 1975). The paired Perspex rings were oval, the inner diameters being 5 and 4 mm; they were placed across the medulla with the long axis lying at right angles to the mid line of the medulla. Three different sizes of single Perspex rings were used; they were round and had inner diameters of 4·2, 3·5 and 2·1 mm. The holder of a single ring was attached to a micromanipulator so that the ring could be moved along the ventral surface of the medulla in both longitudinal and lateral directions, in order to investigate in the same experiment the effect of applying drugs to different areas of the surface. The volume of drug solution placed into each ring was 10–30 μl.

To determine the exact areas reached by the drugs when placed inside the paired rings they were filled at the end of the experiment with 0·8% Bromophenol Blue solution; a few minutes later the cat was killed by an overdose of sodium pentobarbitone I.V. Before the rings were removed they were washed out with 0·9 % NaCl solution and the stained areas at the ventral surface were measured with a divider, using as references the caudal border of the trapezoid bodies and the mid line. In the

experiments in which the holder with a single ring was used and the drug was applied to different areas, the one from which the maximal effect had been obtained was stained with Bromophenol Blue, and from its position those of the other areas were extrapolated.

Drugs used. Atropine methyl nitrate (Sigma), leptazol (pentamethylene tetrazole, Sigma), sodium pentobarbitone (Nembutal sodium powder, Abbott Laboratories). All drugs were freshly dissolved in 0·9 % NaCl solution. The values given in the text for the drugs refer to the salts.

The effects obtained with sodium pentobarbitone were not due to the high pH of the solution since they were not produced by Tris solution of the same pH (9·8); nor were the effects of leptazol the result of hypertonicity since NaCl solutions of 1200 mosM were ineffective.

RESULTS

Bilateral application of leptazol and sodium pentobarbitone

During surgical anaesthesia the bilateral application of leptazol (200 mg/ml) to the caudal area of the ventral surface of the medulla oblongata produced a fall in arterial

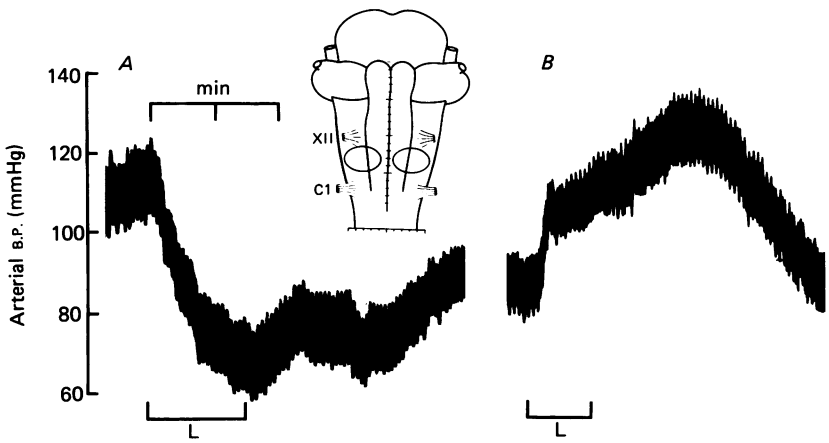

Fig. 1. Arterial blood pressure from a 2·5 kg male cat during surgical anaesthesia produced by intravenous chloralose at 60 mg/kg and given intravenous atropine methyl nitrate at 0·5 mg/kg; between *A* and *B* anaesthesia was deepened by two additional intravenous injections of chloralose at 30 mg/kg. The interval between *A* and *B* was 120 min. Paired Perspex rings placed across the ventral surface of the medulla oblongata for bilateral topical application of leptazol (200 mg/ml) at times indicated by the brackets marked L. The ovals in the inset indicate the areas covered by the rings. Time signal in min.

blood pressure with pronounced bradycardia. This bradycardia was greatly reduced, though not abolished, by an intravenous injection of atropine methyl nitrate at 0·5 mg/kg. It was therefore mainly, but not entirely vagal in origin. The following descriptions of the effects of leptazol and sodium pentobarbitone refer to cats atropinized in this way.

During deepened anaesthesia, which itself produced a slowing of respiration and a gradual fall in arterial blood pressure, the depressor effect of leptazol was converted into a pressor response. This is illustrated in Fig. 1. Fig 1 *A* shows the fall in arterial blood pressure of about 40 mmHg produced by bilateral application of leptazol during surgical anaesthesia and Fig. 1 *B* shows the rise of about 40 mmHg produced by its renewed application to the same area nearly 2 h later during deepened anaesthesia. The first application had produced some slowing of heart rate and of respiration, the second some quickening of heart rate but no change in respiration. In two experiments

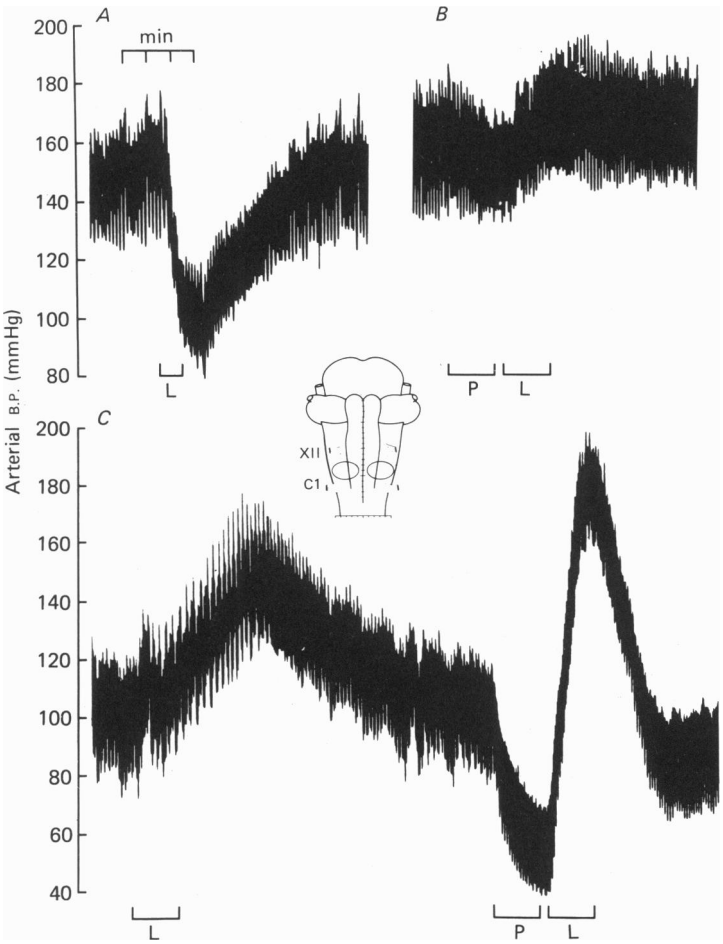

Fig. 2. Arterial blood pressure from a 2·9 kg female cat during surgical anaesthesia produced by intravenous chloralose at 60 mg/kg and given intravenous atropine methyl nitrate at 0·5 mg/kg; between *B* and *C* anaesthesia was deepened by two additional intravenous injections of chloralose at 30 mg/kg. The interval between *A* and *B* was 40 min and between *B* and *C* 200 min. Paired Perspex rings placed across the exposed ventral surface of the medulla oblongata for topical application of leptazol (200 mg/ml) (L) and sodium pentobarbitone (30 mg/ml) (P) as indicated by the bars marked L and P respectively. The ovals in the diagram of the inset indicate the areas covered by the rings; the cat was breathing spontaneously during *A* and *B* but was artificially ventilated during *C* and *D*. Time signal in min.

the slowing of respiration led to respiratory arrest requiring artificial ventilation until spontaneous respiration returned after removal of the leptazol from the rings.

The depth of anaesthesia also affected the response to bilateral application of sodium pentobarbitone. During surgical anaesthesia it produced pronounced tachypnoea but scarcely any change in blood pressure; during deepened anaesthesia it produced tachypnoea and a fall in arterial blood pressure. For instance, in the experiment of Fig. 2 sodium pentobarbitone applied bilaterally during surgical

anaesthesia (*B*) had scarcely any effect on blood pressure but applied during deepened anaesthesia (*D*) it produced a fall of about 50 mmHg.

Interaction between leptazol and sodium pentobarbitone. The response to leptazol was affected by a preceding application of sodium pentobarbitone to the same region, and this effect was again influenced by the depth of anaesthesia. The depressor response to leptazol obtained during surgical anaesthesia was reduced, abolished and sometimes converted into a weak pressor response by a preceding application of sodium pentobarbitone whereas the pressor response to leptazol obtained during deepened anaesthesia was potentiated by it. For instance, in the beginning of the experiment shown in Fig. 2, during surgical anaesthesia, the fall in arterial blood pressure of 50 mmHg produced by the topical application of leptazol (200 mg/ml) (*A*) no longer occurred (*B*) when the leptazol application was preceded by an application of sodium pentobarbitone (30 mg/ml); blood pressure actually rose a little. The fall in blood pressure (*A*) was associated with slowing of heart rate from 250 to 225/min and of respiration from 13 to 9/min. The application of sodium pentobarbitone at *B*, which by itself had scarcely any effect on arterial blood pressure, caused an increase in heart rate from 225 to 265 beats/min and an increase in respiratory rate from 15 to 21/min. With the subsequent leptazol application heart rate increased further to 284/min but respiratory rate fell to 13/min. Later on in the experiment, during deepened anaesthesia, the topical application of sodium pentobarbitone produced a fall in arterial blood pressure, and the pressor response to the subsequent leptazol application was enhanced (*C*). The rise in mean arterial blood pressure in response to the leptazol application was 65 mmHg (from 100 to 165 mmHg) before but 135 mmHg (55–185 mmHg) after the application of sodium pentobarbitone.

Unilateral application of leptazol and sodium pentobarbitone

Many of the results obtained with bilateral application of leptazol were reproduced with its unilateral application, which in addition allowed a more precise localization of the responsive area.

Fig. 3 illustrates the results of an experiment during deepened anaesthesia. Leptazol (200 mg/ml) was applied unilaterally to three areas indicated by the circles in the inset diagram. *A* shows a fall in arterial blood pressure of just over 40 mmHg produced by leptazol applied to the most cranial area represented by the circle nearest to the rootlets of the twelfth cranial nerve. This area corresponds to the nicotine-sensitive area from which in previous experiments the depressor effect had been obtained on applying leptazol (Guertzenstein & Lopes, 1984). The fall in arterial pressure which was associated with a bradycardia from 202 to 168/min, might have been greater during surgical anaesthesia since the fall produced from this area was found to be attenuated by deepening the anaesthesia. Next the leptazol was applied to the most caudal of the three areas, lying just caudal to the rootlets of the first cervical nerve. As shown in Fig. 3*B* blood pressure was not affected. Nor, (as was shown in other experiments) would it have been affected if leptazol had been applied to this region during surgical anaesthesia. Finally, the leptazol was applied to an area between the rootlets of the twelfth cranial and the first cervical nerve. As shown in Fig. 3*C* leptazol now produced a rise of over 80 mmHg which was associated with an increase in heart rate from 240 to 258/min.

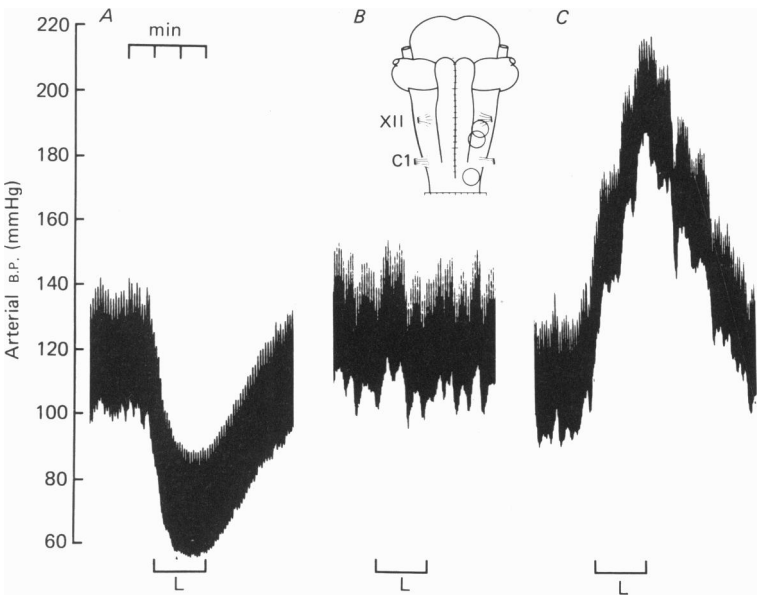

Fig. 3. Arterial blood pressure from a 3·8 kg female cat in deepened anaesthesia produced by intravenous chloralose and given intravenous atropine methyl nitrate at 0·5 mg/kg. Interval between *A* and *B* 90 min and between *B* and *C* 20 min. Application by a single Perspex ring, of leptazol (200 mg/ml) (L), as indicated by the bars marked L, to three areas of the ventral surface of the medulla oblongata indicated in the inset. Leptazol applied at *A* to the area represented by the most cranial circle, at *B* to the area represented by the most caudal circle, and at *C* to the area represented by the middle circle. Time signal in min.

The diagram of Fig. 4 summarizes results obtained from ten cats during deepened anaesthesia, with leptazol unilaterally applied to different regions of the ventral surface. The areas from which pressor responses were obtained are shown by the circles drawn with continuous lines on the right side whilst the circles drawn with interrupted lines on the left correspond to areas from which no pressor responses were produced, blood pressure remained either unaffected or a depressor response was obtained, as from some of the more cranial areas.

The areas from which pressor responses were obtained lie between the rootlets of the twelfth cranial and first cervical nerves. The actual area is probably smaller than indicated by the circles drawn with continuous lines because the upper portion of the most cranial, and the lower portion of the most caudal circles have to be excluded as being responsible for the pressor responses obtained with the ring in these positions. Further, the circles drawn on the left show that, with one exception, the most caudal region between the rootlets of the two nerves is free from interrupted circles. The exception is an experiment in which, for reasons unknown, no pressor response was obtained with leptazol applied to the area which on the right, corresponds to that of greatest density of circles. The cranial–caudal extent of the area from where pressor responses were obtained with leptazol lies 7–11 mm caudal to the trapezoid bodies. This area is somewhat more caudal than the one from which the depressor response

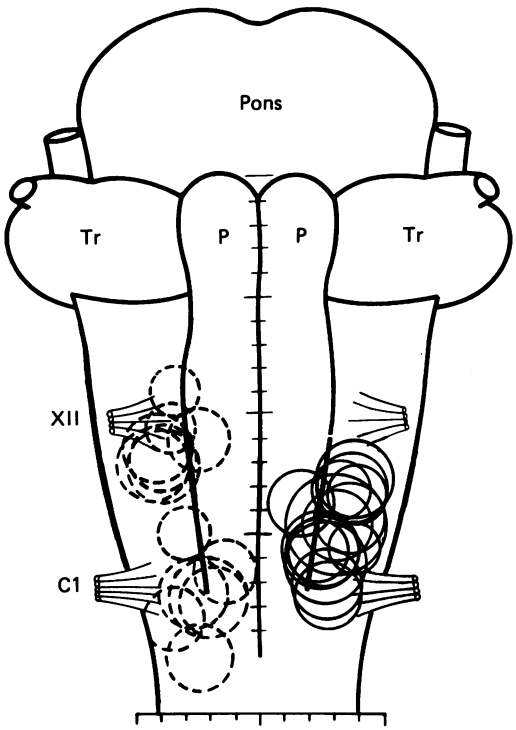

Fig. 4. Diagram of the cat's ventral surface of the medulla oblongata with rootlets of twelfth cranial (XII) and first cervical (C1) nerves. The circles which summarize the results obtained from ten cats in deepened anaesthesia represent areas to which leptazol (200 mg/ml) was applied through single Perspex rings having different diameters. Whether application was actually on the right or the left side, the circles on the right drawn with continuous lines represent areas from where a pressor response was obtained, whereas the circles drawn with interrupted lines on the left represent areas from where no pressor responses were obtained. Each circle is the outcome of a single application but more than one area was examined in the same experiment. Tr, trapezoid bodies; P, pyramids; scales in mm.

had been produced with leptazol previously and which had been found to lie 5–9 mm caudal to the trapezoid bodies (Guertzenstein & Lopes, 1984). There is thus partial overlapping of the two areas.

The potentiation by sodium pentobarbitone of the pressor response to leptazol seen on bilateral application during deepened anaesthesia was also obtained when the drugs were applied unilaterally as shown in Fig. 5. This Figure also illustrates that not all pressor responses obtained from adjacent areas were potentiated; those obtained from the more caudal areas were unlikely to be potentiated. In the experiment of Fig. 5 the drugs were applied to the three areas indicated in the diagram by the circles. The top records show that the response obtained from the area represented by the middle circle was potentiated; the middle records obtained after the ring was moved to the area represented by the most caudal circle show that the somewhat stronger pressor response obtained from this area was not potentiated; finally, the bottom records obtained after the ring had been moved back cranially

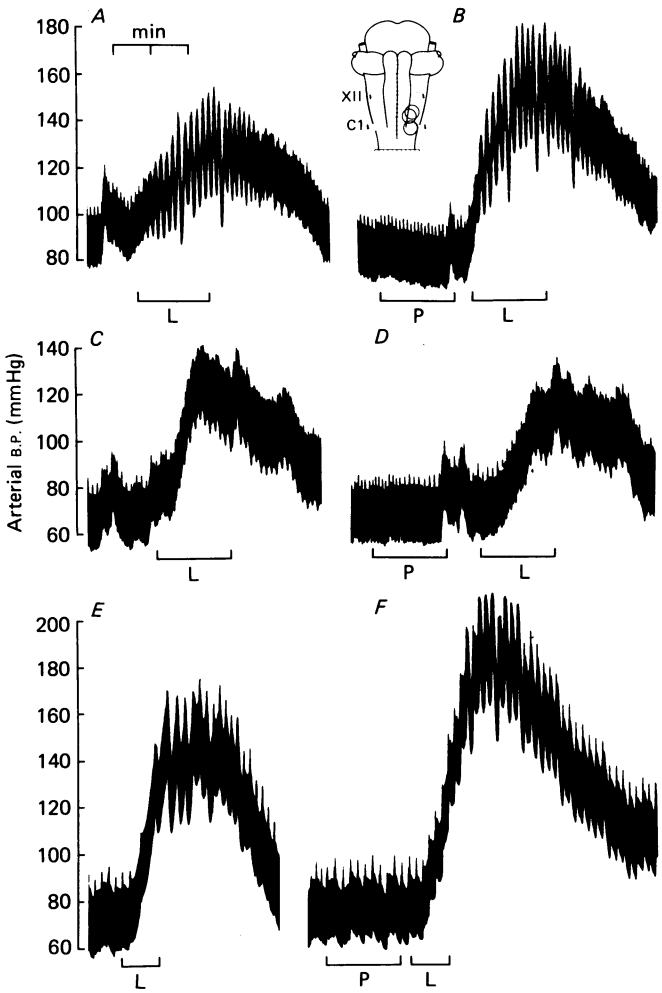

Fig. 5. Arterial blood pressure from a 3·1 kg female cat in deepened anaesthesia produced by intravenous chloralose and given intravenous atropine methyl nitrate at 0·5 mg/kg. Intervals between *A* and *B* 15 min, between *B* and *C* 90 min, between *C* and *D* 10 min, between *D* and *E* 15 min, and between *E* and *F* 8 min. Topical application by a single Perspex ring of leptazol (200 mg/ml) (L) and sodium pentobarbitone (30 mg/ml) (P), as indicated by the horizontal bars marked L and P respectively, to three areas of the ventral surface of the medulla oblongata indicated by the circles in the diagram of the inset. Top records obtained on application to the area represented by the middle circle; middle records to the area represented by the most caudal circle and bottom records to the area represented by the most cranial circle. Time signal in min.

to a position represented by the top circle show that the even stronger pressor response obtained from this area was again potentiated.

With bilateral application, sodium pentobarbitone had been found to produce a fall in arterial blood pressure with pronounced tachypnoea when applied during deepened anaesthesia; unilateral application under otherwise similar conditions had no effect on either blood pressure or respiration (Fig. 5). In two experiments however,

the unilateral application of sodium pentobarbitone produced a lowering of arterial pressure but no tachypnoea.

DISCUSSION

The variations in the blood pressure changes obtained when leptazol was applied to the ventral surface of the medulla oblongata have been resolved. Whether a depressor or a pressor effect was obtained depended on the exact site of application and on the depth of anaesthesia. The area from which a depressor effect was regularly obtained with leptazol, the nicotine-sensitive area, lies about 2 mm more cranial than

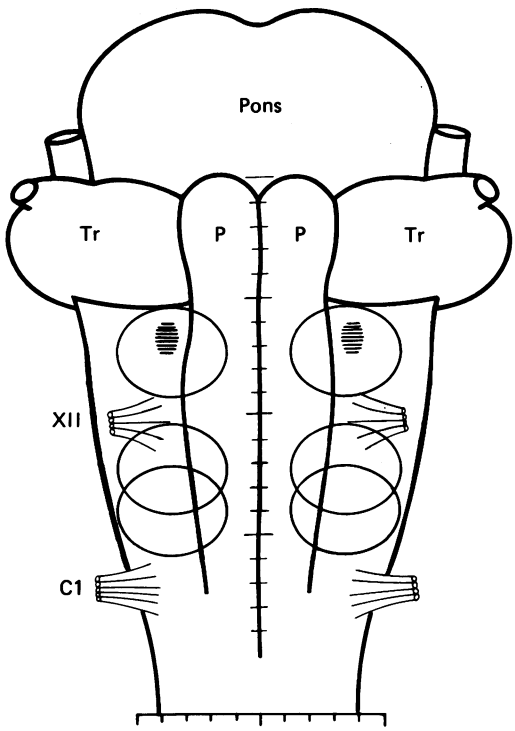

Fig. 6. Diagram of the cat's ventral surface of the medulla oblongata with rootlets of twelfth cranial and first cervical nerves, showing the position of the three areas from which blood pressure effects are obtained on topical application of leptazol. The rostral ovals represent the glycine-sensitive area from which pressor effects and the middle ovals the nicotine-sensitive area from which depressor effects have been obtained previously. The caudal ovals represent the area from which a pressor response to leptazol was obtained in the present experiments during deepened anaesthesia. Tr, trapezoid bodies; P, pyramids. Scales in mm.

the area responsible for the pressor response, and while the depressor response was attenuated during deepened anaesthesia the pressor response to leptazol was obtained during this condition only.

Fig. 6 serves to correlate the results obtained in the present experiments with those described previously. According to the diagram it is possible to distinguish between three areas from which blood pressure effects are evoked with leptazol.

The rostral ovals indicate what has been termed the glycine-sensitive area. When

applied to this area leptazol produces a rise in arterial blood pressure (Guertzenstein, 1973), and sodium pentobarbitone applied bilaterally produces a fall (Feldberg & Guertzenstein 1976). But the actual glycine-sensitive area is much smaller than the area enclosed by the ovals. It is not larger than 1·5 mm^2 (Guertzenstein & Silver, 1974) and is represented in the diagram by the small horizontally striped areas within the ovals.

The middle ovals indicate what has been termed the nicotine-sensitive area (Feldberg & Guertzenstein, 1976). Leptazol applied bilaterally or unilaterally to this area produces a fall in arterial blood pressure, bradycardia and bradypnoea. The fall in arterial pressure is attenuated or abolished by the application of sodium pentobarbitone; the latter by itself produces a small rise in blood pressure with tachycardia and pronounced tachypnoea when applied bilaterally but does not affect blood pressure nor respiration when applied unilaterally (Guertzenstein & Lopes, 1984).

The caudal ovals indicate the area brought to light by the present experiments. It overlaps the one enclosed by the middle ovals. However, in the same way as the actual glycine-sensitive area is smaller than that enclosed by the rostral ovals, so the actual nicotine-sensitive area may be smaller than that enclosed by the middle ovals; similarly, the actual area from which pressor responses to leptazol were obtained in the present experiments may be smaller than that enclosed by the caudal ovals.

The characteristic effect of leptazol applied bilaterally or unilaterally to this area was a pressor response obtained during deepened anaesthesia, and a potentiation of this response by a preceding application of sodium pentobarbitone; the pressor response was associated with some tachycardia and a fall in arterial blood pressure when applied bilaterally; however, when applied unilaterally it did not affect respiration, nor did it usually affect blood pressure, although occasionally a fall occurred as with bilateral application.

The potentiation of the pressor response to leptazol by sodium pentobarbitone may find its explanation in the overlapping of the nicotine-sensitive area with the area from which the pressor response is obtained. Since leptazol applied to the nicotine-sensitive area produces a fall in arterial blood pressure which is abolished by sodium pentobarbitone we only need to assume that the depressor effect is not strong enough to manifest itself as a fall in blood pressure when a pressor response is evoked at the same time from the adjacent area. The depressor effect may merely reduce the pressor response, and removal of this reduction by sodium pentobarbitone would then manifest itself as 'potentiation'. This interpretation is supported by the finding that when pressor responses were obtained with leptazol from adjacent areas by moving the ring in cranial–caudal direction those obtained from the most caudal areas were liable not to be potentiated, probably because in this condition no overlapping occurred with the nicotine-sensitive area.

The area at the ventral surface of the medulla oblongata from which the pressor response to leptazol was obtained in the present experiments appears to be responsible for maintaining arterial blood pressure during deepened anaesthesia. During lighter anaesthesia this function has been attributed to the glycine-sensitive area, for the following reasons. The effects evoked from this area by glycine or sodium pentobarbitone are considered to be the result of an inhibitory action by which some tonic

activity is removed, and the destruction of this area mimics these effects. Whether a drug response results from an excitatory or from an inhibitory action is revealed by a simple criterion. A strong effect obtained on unilateral application is indicative of an excitatory action. But if a drug needs to be applied bilaterally to do so, this is indicative of an inhibiting action (Guertzenstein & Lopes, 1984). Now glycine itself, and also sodium pentobarbitone applied unilaterally to the glycine-sensitive area, have little effect at whatever concentration they are applied; but on bilateral application arterial pressure fails and is no longer maintained. Also, the same happens after unilateral and bilateral destruction of the glycine-sensitive area (Guertzenstein & Silver, 1974).

The conclusion that the area at the ventral medullary surface from which the 'excitatory' pressor response to leptazol was obtained may be responsible for maintaining blood pressure during deep anaesthesia is based on the finding that, in this condition, the application of bilateral sodium pentobarbitone to this area regularly produced a fall in blood pressure; however, on unilateral application this happened only rarely. The fall in blood pressure appears therefore to result from an inhibitory action, from removal of some vasomotor tone still existing in this condition and exerted from this area of the medullary ventral surface. The area enclosed by the caudal ovals in Fig. 6 may thus represent a kind of 'accessory or secondary centre' responsible for maintaining some vasomotor tone during deep anaesthesia.

There is another effect of sodium pentobarbitone which, according to our criterion, may be looked upon as resulting from an inhibitory action, namely the pronounced tachypnoea produced by bilateral but not by unilateral application of sodium pentobarbitone. This tachypnoea was also obtained from the nicotine sensitive area (Guertzenstein & Lopes, 1984). If this tachypnoea were to result from removal of an inhibitory action, it would suggest that during both surgical and deepened surgical anaesthesia respiration is strongly inhibited from the two areas represented by the middle and bottom circles in Fig. 6.

Another effect obtained by topically applied leptazol is the release of vasopressin into the circulation, which is apparently evoked from the same area as the rise in arterial blood pressure produced by leptazol. Therefore, if we attribute the pressor response to an action on structures in the area shown by the caudal ovals in Fig. 6 we must do the same for the vasopressin release evoked not only by leptazol but also by other substances, and probably also for the inhibition of vasopressin release produced by yet another group of substances similarly applied (Feldberg & Rocha e Silva, 1981).

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