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COMPARISON OF THE HYPERGLYCAEMIC EFFECT OF ADRENALINE AND MORPHINE INTRODUCED INTO THE LIQUOR SPACE

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SUMMARY

1. In unanaesthetized cats a comparison is made of the hyperglycaemic effects of adrenaline and morphine, when injected or infused through chronically implanted cannulae, into different regions of the cerebral ventricles or of the subarachnoid space, in order to determine their sites of action.

2. On injection into the cerebral ventricles both adrenaline and morphine have to reach the subarachnoid space beneath the ventral surface of the brain stem before they can exert their hyperglycaemic effect. The adrenaline has to reach the region rostral to the pons, i.e. the fossa interpeduncularis, and the morphine the region caudal to the trapezoid bodies. These conclusions are based on the following findings.

3. When adrenaline (55 μg) and morphine (0·75 mg) were infused into one or other of these two regions, adrenaline produced strong hyperglycaemia on infusion into the fossa interpeduncularis, but had scarcely any hyperglycaemic effect on infusion into the region caudal to the trapezoid bodies. The reverse result was obtained with morphine.

4. It is concluded that the adrenaline hyperglycaemia is mainly a peripheral effect. It occurs after the adrenaline has been absorbed into the bloodstream from the fossa interpeduncularis but an additional central component, an action on brain stem structures reached from the fossa interpeduncularis, cannot be excluded. The morphine hyperglycaemia is a central effect due to an action on superficial structures of the ventral surface of the medulla oblongata, caudal to the trapezoid bodies.

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INTRODUCTION

In cats morphine and adrenaline produce hyperglycaemia when injected into the cerebral ventricles, but both substances must first pass into the subarachnoid space and reach the ventral surface of the brain stem before they are able to produce hyperglycaemia (Sproull, 1963*b*; Feldberg & Gupta, 1974). There the similarity ends. The morphine hyperglycaemia is entirely a central effect and is depressed in anaesthesia. The adrenaline hyperglycaemia is readily obtained in anaesthesia. It is partly a peripheral effect which occurs after the adrenaline has been absorbed into the blood stream, but it is thought to be partly central in origin. The present experiments show that the site on the ventral surface where morphine acts is different from the site where adrenaline is thought to act and where its absorption occurs.

The hyperglycaemic effect of small doses of morphine when injected into the cerebral ventricles of unanaesthetized cats was first described by Borison, Fishburn, Bhide & McCarthy (1962). They concluded that morphine acted on structures lining the walls of the third ventricle. This site was excluded in more recent experiments (Feldberg & Shaligram, 1972; Feldberg & Gupta, 1974) because morphine was shown to produce hyperglycaemia when it did not enter the third ventricle, i.e. on injection into the aqueduct or into the fourth ventricle, or when it did not enter any part of the ventricular cavities, i.e. on injection into the subarachnoid space, either into the cisterna magna or beneath the ventral surface of the brain stem. It was suggested that morphine acted on structures near the ventral surface of the brain stem. These structures are reached more readily by morphine injected intraventricularly than when injected into the cisterna magna, because cats have no foramen of Magendie, which exists in primates only. This would explain why morphine was found to be more potent on intraventricular injection (Feldberg & Gupta, 1974).

The hyperglycaemic effect of adrenaline introduced into the liquor space was first described by Leimdorfer, Arana & Hack (1947) and thought to be central in origin. However, in rabbits it was found by Hasselblatt & Sproull (1961) to be entirely a peripheral effect, as it persisted after division of the greater splanchnic nerves. In cats, the hyperglycaemia was thought to be partly central, partly peripheral in origin. The initial hyperglycaemia of rapid onset was thought to be central in origin because it was abolished by splanchnicotomy whereas the hyperglycaemia that persisted after splanchnicotomy was attributed to a peripheral action which occurred after the adrenaline was absorbed into the blood stream. It developed more slowly but reached the same maximum (Sproull, 1963*a*).

Although both adrenaline and morphine have to pass into the subarachnoid space and to reach regions beneath the ventral surface of the brain stem in order to produce hyperglycaemia, Hasselblatt & Sproull (1961) found that adrenaline (unlike morphine) was more effective when injected into the cisterna magna, than when injected into a lateral ventricle. Later Sproull (1963*b*) compared the effectiveness of 25 μg adrenaline administered into different parts of the liquor space. No hyperglycaemia occurred on injection into the third ventricle or into the cisterna terminalis which lies rostral to the optic chiasma. A moderate degree of hyperglycaemia occurred when the adrenaline was dropped into the opened cisterna magna, and a greater degree of hyperglycaemia was obtained on its injection into the fourth ventricle, but the strongest hyperglycaemia was produced on injection into the fossa interpeduncularis which lies rostral to the pons. Sproull therefore concluded that before the adrenaline could act it had to reach this region where it was absorbed through the pars tuberalis of the hypophysis and where it exerted its central action on the caudal tuber cinereum.

Since previous experiments in cats on the hyperglycaemic effect of adrenaline injected into the cerebral ventricles or into the subarachnoid space were carried out in anaesthesia, it was thought necessary to find out if the differences in its efficacy on injection into different regions of the liquor space could be obtained in the unanaesthetized cat as well. The hyperglycaemic effect of adrenaline and morphine was then compared when injected into the subarachnoid space, either into the fossa interpeduncularis or caudal to the trapezoid bodies. If morphine were to act like adrenaline from the fossa interpeduncularis it should be more potent on injection into the fossa. However, it was found to be more potent when injected caudal to the trapezoid bodies, whereas adrenaline was found to be less effective when injected in this way.

Some of the results have been communicated to the Physiological Society (Dey, Feldberg & Wendlandt, 1974).

METHODS

Cats of either sex weighing between 3 and 3·8 kg were used. For introducing adrenaline or morphine into different parts of the liquor space, a Collison cannula, as modified by Mr A. R. J. Collins, and described previously (Feldberg & Shaligram, 1972), was implanted or fixed to the back of the skull under pentobarbitone sodium (36 mg/kg I.P.) anaesthesia in an aseptic operation. The cat, lying on its belly, had its head fixed to the ear bars and mouthpiece of a stereotaxic instrument. With the exception of cannulation of the lateral cerebral ventricle, the Collison cannula to be implanted was held by a micromanipulator at the correct angle so that it could be moved millimetre by millimetre. The cannula to be inserted into the lateral ventricle was screwed into the skull through a burr hole whereas the cannulae inserted into

the fourth ventricle and into the subarachnoid space beneath the ventral surface of the brain stem were inserted through an opening of about 8 × 10 mm made in the skull with a drill and nibbling forceps. The cannulae were fixed to the skull by acrylic cement and, except for the cannula implanted into the lateral ventricle, further fixation was obtained by enveloping with acrylic cement two small stainless steel screws inserted into the skull, one on each side of the hole.

The details of the procedures varied with the different implantations. For implantation of the cannula into the left lateral ventricle, they were the same as described by Feldberg & Shaligram (1972) and for implantation into the fourth ventricle, they were the same as described by Feldberg & Gupta (1974).

For implantation of the cannula into the fossa interpeduncularis a cannula with a shaft 27 mm long was inserted between the cerebral hemispheres in the mid line, 1 mm posterior to the coronal suture at an angle of 33° directed posteriorly and lowered until the tip hit the bone. This happened when the cannula had been inserted 26–27 mm beyond the dura. The cannula was then withdrawn 0·5 mm. Before insertion of the cannula its rubber cap had been pierced by a needle attached to a syringe filled with 0·9 % NaCl solution. When the cannula was in position and the syringe held vertically, the saline solution could be observed flowing from the syringe. After fixing the cannula to the skull, the cap was removed. A stillete was inserted into the shaft of the cannula so as to keep it patent, and the cap was then replaced. The diagram in Fig. 3*A* shows the position of the cannula.

For implantation of the cannula into the region of the subarachnoid space caudal to the trapezoid bodies a cannula with a shaft 37 mm long was inserted between the cerebral hemispheres about 1 mm lateral to the mid line and 12·5 to 13·5 mm anterior to the interaural line at an angle of 33° directed posteriorly and lowered until the tip hit the bone. This happened when the cannula had been inserted 35·5 to 36·5 mm beyond the dura. The cannula was then withdrawn 0·5 mm. In all other details the implantation was similar to that of the fossa interpeduncularis. The diagram in Fig. 3*B* shows the position of the cannula.

For fixing the cannula at the back of the skull so that it ended just above the atlanto-occipital membrane the method described by Feldberg, Gupta, Milton & Wendlandt (1973) was used. This cannula was used not only for intracisternal injections but also for injections beneath the ventral surface of the brain stem caudal to the trapezoid bodies.

The morphine and adrenaline were injected into the cannulated lateral ventricle in a volume of 0·15 ml. followed immediately by an injection of 0·1 ml. 0·9 % NaCl solution. For the injection of the substances into the cisterna magna a fine hollow stainless steel needle was inserted through the cannula fixed to the back of the skull and lowered until it had pierced the atlanto-occipital membrane, as described by Feldberg *et al.* (1973). Attached to the protruding outer end of the needle was a length of fine polythene tubing. The dead space of needle plus tubing which were filled with 0·9 % NaCl solution was 0·14 ml. The drugs were injected through this tubing in a volume of 0·15 ml. and washed in by 0·14 ml. 0·9 % NaCl solution.

The morphine and adrenaline were infused into the fourth ventricle, fossa interpeduncularis and into the region of the subarachnoid space caudal to the trapezoid bodies in a volume of 40 μl. by a microinfusion pump which delivered this volume from a 100 μl. syringe in 4 min 20 sec. For this purpose the stillete was removed from the Collison cannula and a hollow stainless-steel needle inserted instead. Its length was such that when passed through the rubber diaphragm of the cap and fully inserted, it ended just beyond the end of the shaft of the cannula. The needle was connected by a length of fine polyethylene tubing to the syringe of the microinfusion pump, the needle and tubing being filled with the solution to be infused, the syringe with absolute alcohol.

In most experiments the infusions were made in the unanaesthetized cat, but in some they were made during a short-lasting anaesthesia produced by an injection of Althesin (1·1 mg/kg) into a saphenous vein. This produced immediate surgical anaesthesia lasting less than 10 min (Child, Currie, Davis, Dodds, Pearce & Twissell, 1971). Such a short-lasting anaesthesia did not seem to interfere with the hyperglycaemic effect of morphine or adrenaline. Making use of this fact the infusions into the region caudal to the trapezoid bodies were made not only through a cannula chronically implanted into this region, but also by acutely entering this region under Althesin anaesthesia and in aseptic conditions with a fine hollow stainless-steel needle inserted through the cannula chronically fixed to the back of the skull. The hollow needle was longer than that used for intracisternal injections and after having pierced the atlanto-occipital membrane was lowered through the brain stem until it hit the bone; it was then slightly withdrawn before infusion began. It was necessary to keep the head absolutely still during the insertion and subsequent infusion in order to prevent damage to the brain stem by the needle during head movements. Therefore the whole procedure was done during the few minutes of Althesin anaesthesia whilst the cat was lying on its belly with its head raised and held still in, if not otherwise stated, a horizontal position. The diagram in Fig. 4 shows the position of the cannula.

To assess the spread of the morphine and adrenaline in the subarachnoid space when infused into the fossa interpeduncularis and into the region caudal to the trapezoid bodies, 40 μl. of a 0·8 % bromophenol blue solution was infused into these regions under the same conditions. The cat was killed 20 min later under pentobarbitone sodium anaesthesia, the head perfused with 13 % formaline saline solution, the brain removed and the staining of the dura and of the surface of the brain and brain stem observed with the naked eye.

Samples of venous blood for glucose estimation were collected through a catheter inserted aseptically via a femoral vein into the vena cava inferior either at the time of implantation of the Collison cannula or on the day of the actual experiment during a short-lasting Althesin anaesthesia. The methods of insertion of the catheter, of maintaining its patency, collecting the blood samples and estimating their blood glucose content by the glucose oxidase method were in all details the same as described by Feldberg & Shaligram (1972).

Drugs. Morphine sulphate, (−) adrenaline acid tartrate, Althesin (Glaxo CT134) (Glaxo, Greenford, Middx., England). The values for morphine refer to the salt; those for adrenaline to the base, so as to be able to compare them directly with the doses used by Sproull quoted in the introduction of this paper.

RESULTS

Injections of adrenaline into different parts of the liquor space

The results were similar to those previously obtained under anaesthesia except that the greater efficacy on injection into the cisterna magna in comparison to injections into a lateral ventricle was not so pronounced.

On injection into the cisterna magna or into a left lateral ventricle adrenaline in doses smaller than 100 μg had no effect on the blood glucose level, but doses greater than 200 μg regularly produced hyperglycaemia which lasted for a few hours and varied from cat to cat. A comparison was made in six cats of the effect produced by 220 μg injected one day into

the cisterna magna and on another day into a lateral ventricle. In four cats the cisternal injection was more effective, in one cat there was no difference and in one cat the injection into the lateral ventricle produced a greater

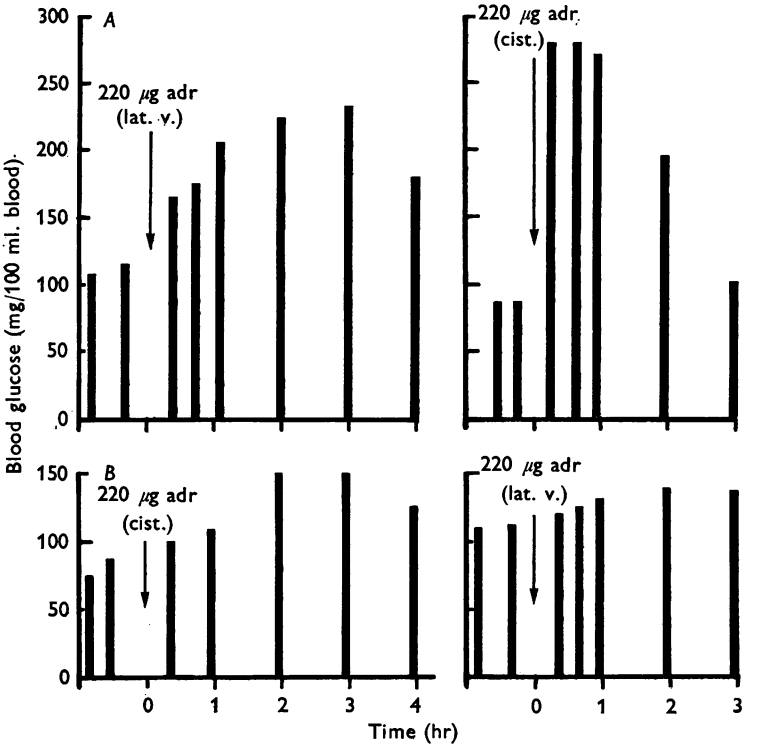

Fig. 1. Effect on blood glucose in two unanaesthetized cats, *A* and *B*, of 220 μg adrenaline injected into the cisterna magna (cist.) or into the left lateral ventricle (lat. v.). Interval between the injections 48 hr. In this and the following Figures the arrows (↓) at zero time indicate moments of injection and the vertical columns the time before and after the injections when venous blood samples were taken. Their glucose concentration is given by the height of the columns.

effect. Fig. 1 illustrates in two cats the greater efficacy of cisternal injections of 220 μg. The one cat (upper records) was relatively sensitive to adrenaline and the injection into the lateral ventricle was given first. The other cat (lower records) was relatively insensitive to adrenaline and the cisternal injection was given first.

On infusion into the fourth ventricle adrenaline was more potent than on injection either into a lateral ventricle or into the cisterna magna and a good hyperglycaemia of rapid onset was regularly obtained with 220 μg,

but 55 μg were ineffective. These facts are illustrated in Fig. 2. The top records obtained from one cat show that 55 μg had no effect on the blood glucose level but that 220 μg produced a strong hyperglycaemia of rapid

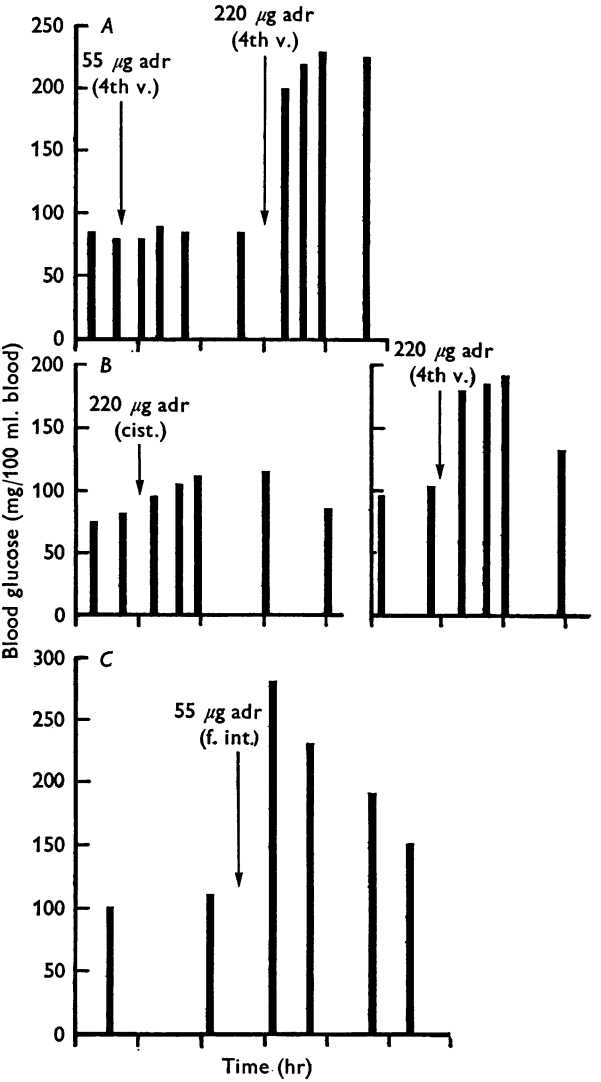

Fig. 2. Effect on blood glucose in three unanaesthetized cats, *A*, *B* and *C*, of 55 and 220 μg adrenaline infused or injected into different parts of the liquor space. In cat *A*, infusion of 55 μg and 48 hr later of 220 μg into fourth ventricle (4th v.). In cat *B*, injection of 220 μg into cisterna magna (cist.) and 48 hr later infusion of 220 μg into fourth ventricle (4th v.). In cat *C*, infusion of 55 μg into fossa interpeduncularis (f. int.).

onset on injection into the fourth ventricle, and the middle records, obtained from another cat, show that 220 μg injected into the cisterna magna was not as effective as when injected into the fourth ventricle.

On infusion into the fossa interpeduncularis, adrenaline was found to be more effective than on infusion into the fourth ventricle. A dose of 55 μg produced regularly strong hyperglycaemia of rapid onset (Fig. 2).

Comparison of infusions of morphine and adrenaline into the fossa interpeduncularis and into the region caudal to the trapezoid bodies

For this comparison the chosen dose for morphine was 0·75 mg and for adrenaline 55 μg. The previous finding of Feldberg & Shaligram (1972) and Feldberg & Gupta (1974) was confirmed that a dose of 0·75 mg morphine produced strong hyperglycaemia on injection into a lateral or into the fourth ventricle, but was too small to be effective on injection into the cisterna magna. A dose of 55 μg of adrenaline was shown in the previous section to be too small to affect the blood glucose level when injected into any part of the ventricular system or into the cisterna magna, but to produce strong hyperglycaemia on infusion into the fossa interpeduncularis.

In eight cats 0·75 mg of morphine was infused into the fossa interpeduncularis. Only in one cat, in the first experiment, did the infusion produce strong hyperglycaemia, with a rise in the blood glucose level from 88 to 268 mg/100 ml. In the subsequent seven experiments a relatively insignificant hyperglycaemia was produced by the infusion, with a rise in the blood glucose level from between 77 and 106 (mean 90) to between 99 and 147 (mean 126) mg/ml. The strong hyperglycaemia obtained in the first experiment may have been due to the fact that the morphine had spread caudally along the ventral surface of the brain stem to the distal end of the medulla oblongata. This was suggested by the staining when bromophenol blue was infused at the end of the experiment before the cat was killed. Deep staining of the dura was found extending from just caudal to the sella turcica to the end of the occipital plate. This did not happen in the other seven experiments. In five of them the staining of the dura after the bromophenol blue infusion was more or less restricted to the region corresponding to the fossa interpeduncularis, and in two no staining was visible. It is probable that in these two the tip of the needle had pierced a small vessel because the fossa contains many thin-walled venous blood vessels of large volume.

In two of the seven cats in which the infusion of 0·75 mg morphine produced a relatively insignificant rise in blood glucose, the infusion of 55 μg adrenaline, made on another day, produced strong hyperglycaemia. The result of one of the two experiments is shown in Fig. 3*A* and illustrates

the much stronger hyperglycaemic effect of 55 μg adrenaline than of 0·75 mg morphine with this route of administration.

The opposite result was obtained when the two substances were infused in these doses into the more caudally situated region of the subarachnoid space beneath the ventral surface of the brain stem, i.e. caudal to the trapezoid bodies. The results were the same on infusion of morphine and adrenaline into this region without anaesthesia through a chronically implanted cannula (seven cats) or during short-lasting Althesin anaesthesia through an acutely inserted cannula (five cats).

In all twelve cats the infusion of 0·75 mg morphine caudal to the trapezoid bodies produced strong hyperglycaemia with a rise in the blood glucose level from between 76 and 120 (mean 98) mg/100 ml. to between 195 and 326 (mean 268) mg/100 ml. In four of these cats 55 μg of adrenaline was infused on another day, in two through the chronically implanted cannula into this region, in two by acutely inserting a hollow needle through the guide cannula ending above the atlanto occipital membrane. The adrenaline infusion produced a mild or very mild hyperglycaemia. The blood glucose rose from between 100 and 114 (mean 105) mg/100 ml. to between 112 and 159 (mean 135) mg/100 ml.

The difference between the efficacy of 0·75 mg morphine and 55 μg adrenaline when infused in the same cat with either the one or the other method of infusion is illustrated in Figs. 3*B* and 4. In the experiment of Fig. 3*B*, infusion was through a chronically implanted cannula and the blood glucose rose after the morphine infusion from 95 to 326 mg/100 ml. but after the adrenaline infusion only from 100 to 112 mg/100 ml. In the experiment of Fig. 4, infusion was through an acutely inserted cannula during an Althesin anaesthesia, and the blood glucose rose after the morphine infusion from 119 to 295 mg/100 ml. but after the adrenaline infusion only from 104 to 114 mg/100 ml.

In all twelve experiments the points where the ventral surface of the brain stem was pierced were lying at or close to the mid line and 1–6 mm caudal to the trapezoid bodies, or at their caudal border. In two of the experiments with the chronically implanted cannulae they were lying at the border, in the other five 1–2 mm, and in the four experiments with the acutely inserted cannulae 3·5–6 mm caudal to the trapezoid bodies.

The staining after bromophenol blue infusion appeared to be different from that observed in the experiments with infusion into the fossa interpeduncularis. In these the dye was mainly taken up by the dura which became deeply stained. In the twelve experiments in which the infusion was caudal to the trapezoid bodies, this happened only in three, in the other nine the dye was mainly taken up by the pia and blood vessels probably because in this region the subarachnoid space is so narrow that

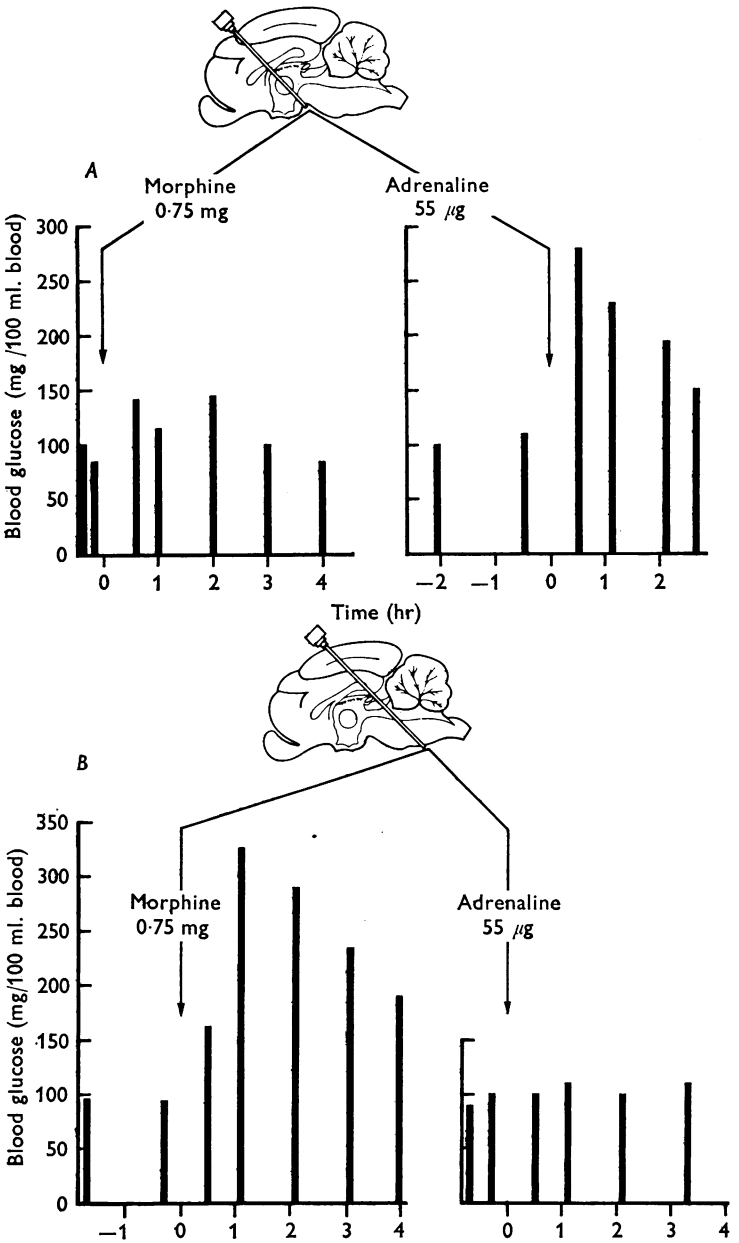

Fig. 3. Effect on blood glucose in two unanaesthetized cats, *A* and *B*, of infusions of 0·75 mg morphine and of 55 μg adrenaline into the subarachnoid space beneath the ventral surface of the brain stem into the fossa interpeduncularis (cat *A*) and caudal to the trapezoid bodies (cat *B*). The diagrams of the midsagittal sections of the cat's brain, given on top of the records, indicate the position of the implanted Collison cannula with its tip in cat *A* in the fossa interpeduncularis and in cat *B* caudal to the trapezoid bodies.

the tip of the needle has partly remained in the nervous tissue and the dye was unable to diffuse rapidly away from the infusion site. In all twelve experiments deep staining was present in a region caudal to the trapezoid bodies close to the tip of the cannula, less intense staining occurred in a wider area, the extent of which varied from experiment to experiment, and in a few experiments there was deep staining along the needle tract of the cannula, with or without staining of the floor of the fourth ventricle.

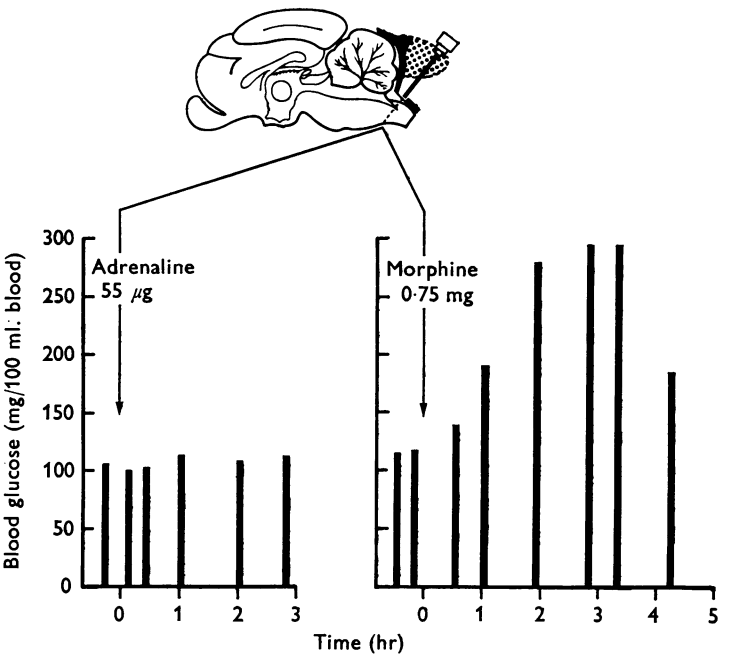

Fig. 4. Effect on blood glucose in an unanaesthetized cat of infusions of 55 μg adrenaline and 4 hr later of 0·75 mg morphine into the subarachnoid space beneath the ventral surface of the brain stem caudal to the trapezoid bodies. The diagram of the midsagittal section of the cat's brain shows the position of the cannula fixed to the back of the skull (in black) with dental cement (dotted area) and the tip resting above the atlanto-occipital membrane. For infusion a hollow needle is inserted through this cannula below the brain stem, as indicated by the interrupted line. The hollow needle was removed immediately after infusion. Injections and infusions were made during short-lasting althesin anaesthesia.

In one cat in which the otherwise correctly implanted cannula had not reached the ventral surface of the brain stem but had ended about 2 mm away from it, the infusion of 0·75 mg morphine produced a relatively mild hyperglycaemia and the blood glucose rose from 104 to 143 mg/100 ml. This finding supports the idea that the structures on which morphine

acts when producing its strong hyperglycaemic effect are mainly situated close to or at the ventral surface.

In another cat, in which the cannula had been implanted incorrectly and its tip had pierced the ventral surface of the brain stem in the middle of the pons, the infusion of 0·75 mg morphine produced a mild hyperglycaemia; the blood glucose rose from 87 to 127 mg/100 ml. This finding suggests that the region where morphine acts when producing its strong hyperglycaemia lies caudal to the pons since in the region of the upper brain stem the flow of c.s.f. is directed mainly rostral in direction. This was evident from the staining after infusion of bromophenol blue. There was deep staining of the pons and of the ventral surface of the cerebrum rostral to it, but the trapezoid bodies and the regions caudal to it were found to be stained faintly. In yet another experiment the 0·75 mg of morphine was infused during a short-lasting Althesin anaesthesia through an acutely inserted cannula, but during the insertion as well as during the morphine infusion, the head was kept in a maximally flexed position so that the cannula, when passing through the brain stem, pierced the ventral surface 10 mm caudal to the trapezoid bodies near the level of the rootlets of C_1. In this condition the morphine infusion did not affect the blood glucose level, and the staining after infusion of bromophenol blue showed that the dye had passed mainly caudal in direction, and deeply stained the dura covering the first and second vertebrae.

Behavioural effects. Morphine infused into the fossa interpeduncularis or caudal to the trapezoid bodies produced regularly strong shivering and mydriasis which was not maximal after infusion into the fossa, but the strong excitation and the continuous miaowing produced by injections of morphine into a lateral ventricle did not occur. Some restlessness, circling, kneading of the forepaws and salivation were present in a few experiments and when the paws were squeezed after the infusions of morphine caudal to the trapezoid bodies, the cats did not react, suggesting analgesia.

DISCUSSION

Both adrenaline and morphine have to pass into the subarachnoid space beneath the ventral surface of the brain stem before they can exert their hyperglycaemic effect on intraventricular injection. To do so, the adrenaline has to reach the region of the brain stem rostral to the pons, i.e. the fossa interpeduncularis. For adrenaline, therefore, the most effective route of administration is the injection directly into the fossa. This was first shown by Sproull (1963*b*) in anaesthetized cats and has been confirmed in the present experiments in cats which were not anaesthetized. Injected into the subarachnoid space more caudally, i.e. either caudal to the

trapezoid bodies or even only caudal to the pons, the adrenaline was much less effective. The reverse was true for morphine which does not need to reach the region rostral to the pons to produce its hyperglycaemic effect. Morphine was found to be more effective on injection caudal to the trapezoid bodies than on injection into the fossa. So whatever the mode of action of the two substances, they have to reach different regions in the subarachnoid space in order to be able to produce their hyperglycaemic effect.

In rabbits, the hyperglycaemia produced by adrenaline injected into the liquor space is a peripheral effect which is not affected by bilateral splanchnicotomy and occurs after the adrenaline has been absorbed into the blood stream (Hasselblatt & Sproull, 1961). The hyperglycaemia in cats is also partly a peripheral effect, but according to Sproull (1963*a*) there is a central action as well because the hyperglycaemia developed more slowly after bilateral splanchnicotomy which did not affect the hyperglycaemia in response to intravenous adrenaline. The effect of bilateral splanchnicotomy, however, need not result from elimination of a central component. Delayed absorption due to blood pressure changes produced by the splanchnicotomy could account for it and would explain why the hyperglycaemia, though developing more slowly, reached the same maximum. In rabbits adrenaline appears to be more readily absorbed from the liquor space as well as from the abdominal cavity than in cats (Hasselblatt & Sproull, 1961; Sproull, 1963*b*). This better absorption might explain why splanchnicotomy did not affect the development of the hyperglycaemia in rabbits in the same way as it did in cats.

It is thus possible that in cats, too, the hyperglycaemia produced by adrenaline injected into the liquor space is entirely a peripheral effect occurring after its absorption from the fossa interpeduncularis. There would then be no need to assume different mechanisms for rabbits and cats. Nor would it be necessary to postulate two sites on the ventral surface of the brain stem of the cat from where substances produce hyperglycaemia, nor that the action of adrenaline at the one site is resistant to, but the action of morphine at the other site is depressed by anaesthetics. At present it is not possible to say definitely whether two components, a peripheral and a central one, account for the hyperglycaemia which is produced in cats by adrenaline injected into the liquor space, or whether, as in rabbits, the hyperglycaemia is entirely a peripheral effect.

The morphine hyperglycaemia in cats is entirely central in origin due to an action on structures situated near the ventral surface of the medulla oblongata. This localization is based on the findings that the effect was regularly obtained when the injection site in the subarachnoid space was 1–6 mm caudal to the trapezoid bodies or at their caudal border, but that

no hyperglycaemia occurred when the site was more caudal, i.e. at the level of the rootlets of the first cervical nerves, and that usually only a mild hyperglycaemia occurred when the site was more rostral, i.e. in the middle of the pons. A more precise localization was not possible with the methods used, and the method of applying morphine topically to the ventral surface of the brain stem by means of perspex rings was not applicable because the cat has to be anaesthetized for this method, and anaesthesia depresses the morphine hyperglycaemia. In addition, the surgical procedure of exposing the ventral surface of the brain stem itself produces hyperglycaemia. At present, therefore, it cannot be stated whether the site where morphine acts is identical with one or the other of the various 'chemosensitive zones' on the ventral surface of the medulla oblongata where the topical application of drugs produce changes in respiration (Loeschcke & Koepchen, 1958; Mitchell, Loeschcke, Severinghaus, Richardson & Massion, 1963; Trouth, Loeschcke & Berndt, 1973), changes in arterial blood pressure (Schlaefke & Loeschcke, 1967; Feldberg & Guertzenstein, 1972; Guertzenstein, 1973; Bousquet & Guertzenstein, 1973; Edery & Guertzenstein, 1974; Guertzenstein & Silver, 1974), or a release of vasopressin (D. Bisset, W. Feldberg, D. G. Guertzenstein & M. Rocha e Silva Jr, unpublished experiments).

Adrenaline has not only hyperglycaemic properties when injected into the liquor space: on injection into a lateral ventricle it depresses the hyperglycaemia produced by morphine similarly injected (Feldberg & Shaligram, 1972). If the entire hyperglycaemic effect of adrenaline is peripheral in origin, then its central effect on the blood glucose level would be a purely inhibitory one, antagonizing the hyperglycaemic effect of drugs like morphine. This inhibitory action might be on the same structures near the ventral surface of the medulla oblongata on which morphine acts when producing hyperglycaemia.

To produce hyperglycaemia with morphine, larger doses were required on injection into the cisterna magna than on injection into a lateral ventricle (Feldberg & Shaligram, 1972). This was explained by the fact that cats have no foramen of Magendie and that the ventral surface of the brain stem is reached more readily from a lateral ventricle than from the cisterna. Adrenaline also has to reach the ventral surface. Yet adrenaline was not found to be less effective on cisternal injection. On the contrary, in the present experiments on unanaesthetized cats, the cisternal injections produced more often a stronger hyperglycaemia, and in the experiments of Sproull on anaesthetized cats, the introduction of adrenaline into the cisterna was very much more effective than injections into a lateral or the third ventricle. On the other hand, not only morphine, but also adrenaline, was more effective on injection into the fourth ventricle

than on injection into the cisterna. It is therefore necessary to assume that part of the adrenaline injected into a lateral or the third ventricle is prevented from passing into the fourth ventricle and that this does not occur with morphine. One possibility would be that the adrenaline which does not reach the fourth ventricle, has been taken up and destroyed by the ependyma of the lateral and of the third ventricle, or of the choroid plexus, or of the aqueduct. In the aqueduct the disappearance of adrenaline might also be a function of the Reissner fibre which originates from the subcommissural organ at the rostral end of the aqueduct, passes through the aqueduct, the fourth ventricle and then through the whole length of the central canal of the spinal cord. The Reissner fibre has recently been shown to have the property of selectively binding catecholamines (Ermisch, Sterba & Hess, 1970; Hess, Hoheisel & Sterba, 1973; Hess & Sterba, 1973). Whatever the explanation, the fact that substances injected into the cerebral ventricles may disappear on their way to the subarachnoid space has to be taken into account when comparing the efficacy of drugs introduced by different routes into the liquor space and drawing conclusions from such comparisons about the site of their action.

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