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HYPERGLYCAEMIA PRODUCED BY DRUGS WITH ANALGESIC PROPERTIES INTRODUCED INTO THE CEREBRAL VENTRICLES OF CATS

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1 The effects on blood glucose of four substances with analgesic properties (apomorphine, pethidine, codeine and etorphine) and of prostaglandin E_1 were examined in unanaesthetized cats. They were applied by the intraventricular route being either injected into a lateral ventricle or infused into the fourth ventricle through implanted Collison cannulae.

2 Apomorphine gave rise to pronounced hyperglycaemia in a dose of 0.75 mg which produced scarcely any hyperglycaemia on intravenous injection. It was more effective on infusion into the fourth ventricle than on injection into a lateral ventricle and was approximately half as potent as morphine in provoking hyperglycaemia.

3 Codeine produced no hyperglycaemia in doses of 0.75 and 1.5 mg.

4 Pethidine had a weak hyperglycaemic action in doses of 0.75 and 1.5 mg, but the effect was not regularly obtained. Potency of the drug was at most only a third to a sixth that of morphine.

5 Etorphine produced strong hyperglycaemia on infusion into the fourth ventricle in a dose of 10 μg. Unlike apomorphine or morphine it was more potent on injection into a lateral ventricle when it produced a strong hyperglycaemic response in doses of 5 or 1 μg, which were subthreshold on infusion into the fourth ventricle. However, this response may have been brought about indirectly as a result of severe asphyxia and of convulsions associated with the injections. On infusion into the fourth ventricle, etorphine was about 75 times as potent as morphine in producing hyperglycaemia.

6 Prostaglandin E_1 had no hyperglycaemic action when infused into the fourth ventricle in a dose of 400 ng.

Introduction

Morphine injected into the cerebral ventricles of unanaesthetized cats produces hyperglycaemia, an effect first described by Borison, Fishburn, Bhide & McCarthy (1962). The hyperglycaemia is a central effect, but it does not stem from an action on structures in the walls of the third ventricle as suggested by these authors. Recent experiments indicate that the structures on which morphine acts when producing this effect are situated near the ventral surface of the brain stem caudal to the trapezoid bodies and are reached after the drug has passed into the subarachnoid space through the lateral recesses (Feldberg & Shaligram, 1972; Feldberg & Gupta, 1974; Dey, Feldberg & Wendlandt, 1975).

In the present experiments, four other substances with analgesic properties were examined to find out whether they produce hyperglycaemia on injection into a lateral ventricle or on infusion into the fourth ventricle of unanaesthetized cats, and whether there is some correlation between analgesic and hyperglycaemic action. The four substances were apomorphine, pethidine, codeine and etorphine. The first three are less potent analgesics than morphine, whereas etorphine is more potent.

An effect on blood glucose has previously been found with three of them, pethidine, apomorphine and codeine, but only by subcutaneous injection in rabbits. Pethidine in doses up to 20 mg/kg was without effect (Schaumann, 1940) but hyperglycaemia was observed with apomorphine and codeine. Campbell & Morgan (1973) obtained hyperglycaemia with 5 mg apomorphine and attributed the effect to a central action because it was abolished by anaesthesia. Ko (1935) found that apomorphine-induced hyperglycaemia was dose-dependent in doses ranging from 0.5 to 20 mg/kg, that the effect was reduced after bilateral splanchnicotomy and almost abolished by removal of the suprarenals. Hyperglycaemia followed the injection of 2 to 20 mg/kg codeine

and its potency was less than that of morphine (Akimoto, 1933). The effect was abolished after section of the splanchnic nerves or removal of the suprarenals (Ro, 1935/36) as well as by x-ray radiation of the animals (Sai, 1941).

Finally, experiments were carried out with prostaglandin E_1 because Bergström, Carlson & Orö (1966) had found that in dogs, intravenous infusions of this substance at rates of 0.2, 0.4, 0.8 and 1.6 $\mu g\ kg^{-1}\ min^{-1}$ effected a slight increase in blood glucose concentration although the change was statistically significant only with 0.8 $\mu g\ kg^{-1}$ $minute^{-1}$. Further, the suggestion has been made that inhibition of effects of prostaglandin may be involved in morphine actions; this possibility has been discussed in connection with the analgesic action of morphine and its derivatives because compounds belonging to this group were found to inhibit the stimulating action of prostaglandins E_1 and E_2 on cyclic adenosine 3′,5′-monophosphate (AMP) formation in rat brain (Collier & Roy, 1974). On the other hand, both morphine and apomorphine stimulate prostaglandin synthetase derived from bull seminal vesicles or rabbit brain (Collier, McDonald-Gibson & Saeed, 1974).

Methods

Cats of either sex weighing between 3 and 3.8 kg were used. For injections into the left lateral ventricle or for infusions into the fourth ventricle, a Collison cannula was implanted in an aseptic operation under pentobarbitone sodium anaesthesia. The method for cannulating the lateral ventricle was that described by Feldberg & Shaligram (1972), and for the fourth ventricle, that of Feldberg & Gupta (1974). The injections or infusions of drugs were made after recovery from operation, a few days later, without anaesthesia. They were injected into the cannulated lateral ventricle in a volume of 0.15 ml, followed immediately by an injection of 0.05 ml of a 0.9% w/v NaCl solution (saline), or infused in a volume of 40 μl by a microinfusion pump which delivered this volume from a 100 μl syringe in 4 min 20 seconds. Details of the infusion procedures are given by Dey *et al.* (1975). Intravenous injections were made through a saphenous vein.

The actual position of cannulae implanted into lateral or fourth ventricles and the delivery of drugs through them was ascertained at the end of the experiments by injecting or infusing a 0.8% bromophenol blue solution of the same volume as that used for injecting or infusing the drugs through the cannulae. The cats were killed 20 min later during pentobarbitone sodium anaesthesia and the position of the cannulae and the spread of the dye observed with the naked eye. On infusion into the fourth ventricle, no dye appeared to have entered the aqueduct as there was no staining of the peri-aqueductal grey matter; however, there was deep staining of the anterior half of the floor of the fourth ventricle which contrasted with the unstained posterior half. The stained area ceased abruptly in a straight line between the two lateral recesses. There was staining of the ventral surface of the brain stem and cerebellum.

The collection of blood samples from the inferior vena cava and the estimation of their glucose content by a glucose oxidase method were as described previously (Feldberg & Shaligram, 1972).

Drugs

The following drugs were used: morphine sulphate, pethidine hydrochloride (Roche Products Ltd., Welwyn Garden City), codeine phosphate, apomorphine hydrochloride (MacFarlane Smith Ltd., Edinburgh), etorphine hydrochloride (a gift from Dr J.W. Lewis, Reckitt & Colman, Hull). All drugs were dissolved in saline immediately before use. This was particularly important for apomorphine as the solution turned a greenish colour within 10 min and was then inactive. The amounts of the drugs given in the text refer to the salts. Prostaglandin E_1 was a gift from Dr J. Pike, Upjohn & Co., Kalamazoo, Michigan, U.S.A.

Results

Apomorphine

A dose of 0.75 mg produced a strong hyperglycaemic response when injected into a lateral ventricle or infused into the fourth ventricle, but had scarcely any effect on blood glucose level when injected intravenously. The effect is thus a central one. The results obtained in five cats are summarized in Table 1. They show that apomorphine was more effective when infused into the fourth ventricle than when injected into a lateral ventricle. In the three experiments on cats 1 and 2 following injections into a lateral ventricle, the blood glucose concentration rose to between 140 and 146 (mean 143) mg/100 ml, whereas in the three experiments on cats 3, 4 and 5, where infusions were made into the fourth ventricle, it rose to between 183 and 247 (mean 219) mg/100 ml. The last two experiments of the Table show further that 0.75 mg of apomorphine had scarcely any hyperglycaemic action after intravenous injection. This difference in efficacy of

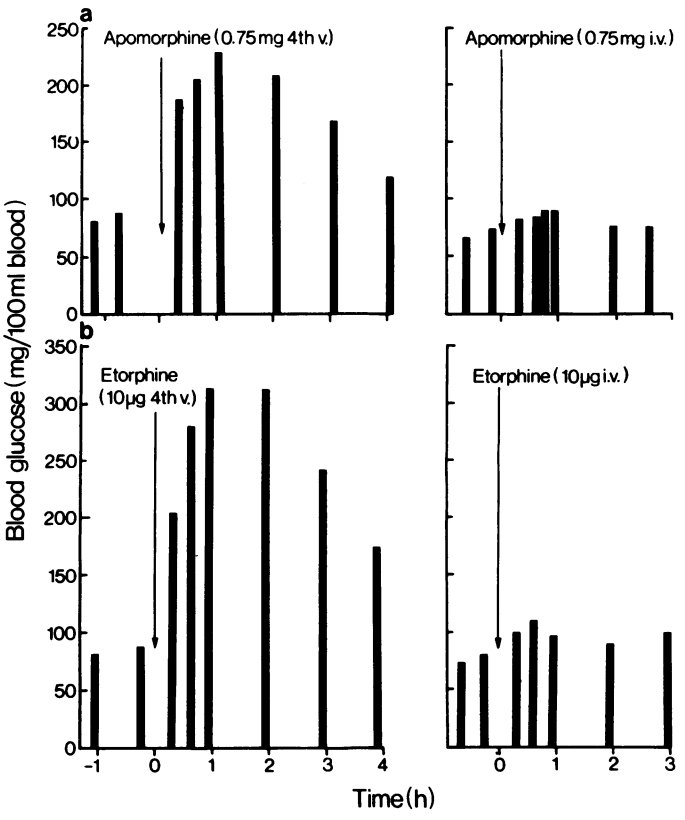

Figure 1 Effects on blood glucose in two unanaesthetized cats. (a) Effect of apomorphine (0.75 mg) infused into fourth ventricle (4th v) and three days later injected intravenously into the same cat. This is cat no. 4 of Table 1. (b) Effect of 10 μg etorphine infused into fourth ventricle (4th v) and 24 h later injected intravenously (i.v.). This is cat no. 14 of Table 2. In this and in Figure 2, the arrows (↓) indicate moment of infusion or injection and the vertical columns time, as shown on the abscissae, before and after introduction of the drugs when venous blood samples were taken. Glucose concentration is given by the height of the columns.

Table 1 Effect of apomorphine (0.75 mg) on blood glucose concentration in unanaesthetized cats

		Blood glucose (mg/100 ml). Min before and after apomorphine administration							
Cat no.	*Route of administration*	*−90 to −45*	*−46 to −5*	*+20*	*+40*	*+60*	*+120*	*+180*	*+240*
1	Lateral ventricle	100	102	143		136	136	136	
1	Lateral ventricle	73	73	140	146	144	92	92	
2	Lateral ventricle	80	88	132	140	132	108	92	
3	IVth ventricle	89	95	174	183	117	130	109	
4	IVth ventricle	80	88	188	206	228	208	168	120
5	IVth ventricle	95	87	213	227	247	182	140	
2	Intravenous	78	70	74	74	76	82	85	
4	Intravenous	64	72	80	84	88	76	76	

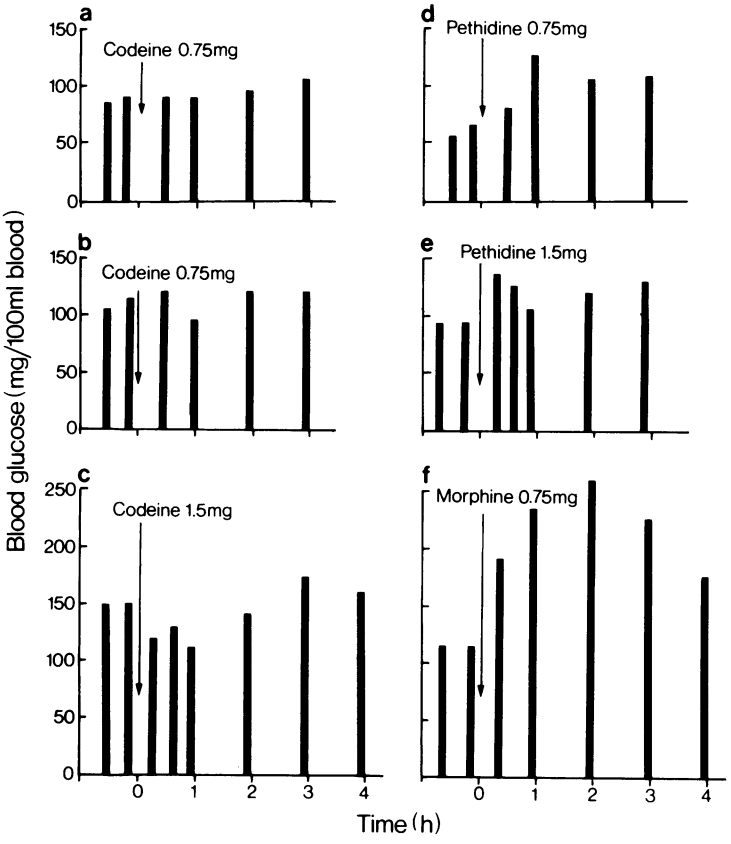

Figure 2 Effects on blood glucose in five unanaesthetized cats: (a) and (d) from the same cat. (a), (b) and (c), Effect of 0.75 and 1.5 mg of codeine, (d) and (e) of pethidine, and (f) of 0.75 mg morphine.

apomorphine introduced into the cerebral ventricles or injected intravenously is also illustrated in Figure 1a. In this cat (no. 4 of Table 1) the drug was first infused into the fourth ventricle and three days later injected intravenously.

When the results are compared with those previously obtained with morphine injected into a lateral ventricle (Feldberg & Shaligram, 1972), it would appear that apomorphine was approximately half as potent in producing hyperglycaemia because 0.75 mg apomorphine was less potent than 0.75 mg, but more potent than 0.24 mg of morphine.

It is known that cats, compared to dogs, are relatively insensitive to the emetic action of apomorphine (Reynolds & Randall, 1957). In the present experiments, 0.75 mg produced the full emetic response consisting of salivation, retching and vomiting in one, and salivation with retching in another cat after injection into the lateral ventricle. Salivation alone occurred also on infusion of apomorphine into the fourth ventricle, began within a few minutes of the injection or infusion and continued for 20 to 45 minutes. During this period the cats were restless and two cats defaecated and urinated. Shivering was regularly produced but began late, 20 to 25 min after the injection or infusion when the periods of restlessness and salivation were over. It then continued for another 20 to 45 minutes.

Codeine and pethidine

Figure 2 illustrates five experiments in which these compounds were injected into a lateral ventricle in a dose of 0.75 or 1.5 mg. Experiments (a), (b) and (c), show that these doses of codeine did not produce hyperglycaemia; in experiments (b) and (c), the injections actually resulted in a transient mild hypoglycaemic state. Pethidine had a weak hyperglycaemic action which was not regularly obtained. In experiment (d), a mild effect was

obtained with 0.75 mg but doubling the dose, as in experiment (e), did not increase it. In two other experiments, the infusion of 1.5 mg into the fourth ventricle produced mild hyperglycaemia in one animal, and none in the other. The mild hyperglycaemia resulting from 0.75 and 1.5 mg in experiments (d) and (e) was of about the same order as that previously observed after 0.24 mg morphine similarly injected (Feldberg & Shaligram, 1972). The hyperglycaemia-producing property would appear therefore to be not more than about a third to a sixth that of morphine.

Experiment (f) of Figure 2 shows, for comparison, the strong hyperglycaemic effect obtained on injection of 0.75 mg morphine hydrochloride into a lateral ventricle. As the sulphate salt of morphine was used in all previous experiments to produce hyperglycaemia on intraventricular injection (Borison *et al.*, 1962; Feldberg & Shaligram, 1972; Feldberg & Gupta, 1974; Dey *et al.*, 1975), this experiment, performed with the hydrochloride, shows that hyperglycaemia is not an effect of the sulphate moiety but of morphine itself.

Of the various behavioural effects seen after intraventricular injection of morphine, only two, shivering and miaowing, occurred with codeine and pethidine, and for much shorter periods than with morphine. With codeine, shivering began about 1 min and with pethidine about 5 min after injection. At first, shivering was strong, widespread and continuous, but within 10 to 25 min it became weaker, intermittent, and then stopped. Miaowing occurred only with the higher dose (1.5 mg). It began about 5 min after codeine and about 20 min after pethidine injection, and lasted for 10-12 minutes. At first, the response was strong and occurred frequently but it became gradually weaker, and the intervals between each miaowing increased before it finally stopped.

Etorphine

Hyperglycaemia was obtained with etorphine in much smaller doses than with apomorphine or morphine, and the drug was more potent on injection into the lateral ventricle than on infusion into the fourth ventricle. On injection into the former, 5 μg and even 1 μg were sufficient to produce a strong hyperglycaemic response, but on infusion into the latter, these doses were subthreshold and it required 10 μg to demonstrate the hyperglycaemic effect. The high potency of etorphine as well as its relative difference in potency when administered by the two routes are evident from the first thirteen experiments shown in Table 2; seven were performed with injections into the lateral ventricle, and six with infusions into the fourth ventricle. The last two experiments of the Table show further that an intravenous injection of 10 μg etorphine, a dose which produced a strong hyperglycaemic response when introduced into either ventricle, had merely a mild hyperglycaemic effect. Figure 1b illustrates this difference in efficacy on the same cat after 10 μg etorphine had first been infused into the fourth ventricle, and 24 h later injected intravenously.

The hyperglycaemic effect of 10 μg etorphine infused into the fourth ventricle was of the same order as previously found for 0.75 mg morphine (Feldberg & Gupta, 1974) given by the same route. Under these conditions, etorphine thus

Table 2 Effect of etorphine on blood glucose concentration in unanaesthetized cats

Cat no.	Route of administration	Dose (μg)	Min before and after etorphine administration: −90 to −45	−46 to −5	+20	+40	+60	+120	+180	+240
6	Lateral ventricle	10	69	76	162	190	157	162	119	
7	Lateral ventricle	10	82	89	227	262	266	217	111	
8	Lateral ventricle	10	111	115	271	315	320	302	235	
9	Lateral ventricle	10	83	79	262	285	333	228	124	
10	Lateral ventricle	5	113	102	258	267	283	220	108	
11	Lateral ventricle	5	100	92	275	350	308	275	171	
11	Lateral ventricle	1	–	88	176	170	170	–	–	
12	IVth ventricle	10	89	89	156	180	208	172	98	
13	IVth ventricle	10	76	82	192	224	228	228	140	88
14	IVth ventricle	10	80	87	204	278	313	313	243	174
15	IVth ventricle	5	63	60	71	95	92	112	83	
12	IVth ventricle	5	88	96	100	102	100	104	88	
13	IVth ventricle	2	84	82	82	86	90	88	100	
14	Intravenously	10	73	82	100	111	95	89	100	
16	Intravenously	10	83	92	100	119	117	120	125	

appears to be about 75 times more potent than morphine.

There were also differences in behavioural response depending on site of introduction. Certain effects were produced when 1, 5 or 10 μg etorphine were injected into a lateral ventricle, but did not occur when these doses were infused into the fourth ventricle. They included severe slowing of respiration leading to asphyxia, short bouts of tonic-clonic convulsions and extreme rigidity of spasm of skeletal muscles lasting for several minutes, greatly impeding respiratory movements and thereby aggravating the asphyxia. The hyperglycaemia produced on injection of etorphine into a lateral ventricle in doses which were subthreshold on infusion into the fourth ventricle, may well have resulted directly from these effects.

Other effects obtained with 10 μg and sometimes with 5 μg etorphine on introduction into either ventricle were constriction of the ear vessels, mild shivering and ataxia lasting about 10 min, and mydriasis and restlessness of longer duration. During the initial period of ataxia, circling movements occurred with the hindquarters flexed so that the cat moved on its belly. Later the animal moved about continuously looking from side to side, and repeatedly jumping against the roof or side of the cage. When jumping against the side of the cage, it clung to it and remained immobile for a few seconds before it fell down. All movements were rapid. Mydriasis quickly became maximal, remained so for about an hour and subsided gradually during the following two hours. The cats did not react to squeezing the paws, suggesting strong analgesia. Some of these effects were also observed after intravenous injection of 10 μg of etorphine which, in addition, produced intense salivation.

Respiratory depression was also obtained when doses larger than 10 μg were infused into the fourth ventricle. When 20 μg were administered in this way, respiration stopped and artificial ventilation by rhythmic compression of the thorax with both hands was applied for 10 to 20 min.

Prostaglandin E_1

Infusions of 400 ng of prostaglandin E_1 into the fourth ventricle produced no hyperglycaemia but merely strong shivering, the usual effect of this drug when given by the intraventricular route.

Discussion

The present experiments show that apomorphine, pethidine and etorphine, but not codeine, share with morphine the property of producing hyperglycaemia when applied by the intraventricular route; the hyperglycaemia is a central effect because it was obtained with doses which were ineffective on intravenous injection. This was shown for apomorphine, but was not examined for pethidine as it has only a weak and irregular hyperglycaemic effect. No experiments were done to determine the site of action of these substances although it is probably the same as that on which morphine acts when producing its hyperglycaemic effect, i.e. the ventral surface of the brain stem (Dey *et al.*, 1975). When injected or infused into the cerebral ventricles it therefore has to pass through the lateral recesses into the subarachnoid space before it can act. The finding that morphine is more effective when infused into the fourth ventricle instead of being injected into a lateral one is also readily explained by such a site of action. In the present experiments, apomorphine was also more effective on infusion into the fourth, than on injection into a lateral ventricle. However, the reverse was true for etorphine. On injection into a lateral ventricle, it produced hyperglycaemia in doses that were subthreshold on infusion into the fourth ventricle. However, this hyperglycaemia is probably brought about indirectly through the severe asphyxia and/or convulsions produced by these injections. Otherwise two sites of action would have to be proposed, one on the ventral surface being the site where apomorphine and morphine act, and another in the walls of the cerebral ventricles rostral to the fourth ventricle, a site not acted upon by either drug.

When comparing the hyperglycaemic potency of the four analgesic drugs examined with that previously obtained for morphine when injected into a lateral or infused into the fourth ventricle (Feldberg & Shaligram, 1972; Feldberg & Gupta, 1974), it would appear that apomorphine is about half, and pethidine at most about a third to a sixth as potent as morphine. With codeine no hyperglycaemia was obtained but if its potency were about a tenth that of morphine, no effect would have been detected with the sensitivity of the method used. On the other hand, etorphine was much more potent than morphine and, based on the results obtained after infusion into the fourth ventricle, it would appear to be about 75 times more potent.

Thus it is evident that there is some correlation between hyperglycaemia and analgesic action of these substances, for apomorphine, pethidine and codeine are less potent analgesics, and etorphine is much more potent than morphine.

To correlate the two actions is justified because analgesia, too, appears to be produced by an action on structures on the ventral surface of the brain stem. However, to assess the relative

potencies of the two actions of the various substances more quantitatively, it would be necessary to compare them in the same species and with the same method of administration.

The evidence for an action on the ventral surface of the brain stem is similar for the analgesic as for the hyperglycaemic action although the structures involved are unlikely to be the same. Herz, Albus, Metys, Schubert & Teschemacher (1970) studied in rabbits the analgesic effect of morphine injected into different parts of the ventricular system. They found it to be most effective when injected into the aqueduct or fourth ventricle and concluded that morphine produced analgesia by an action on structures in their walls. They did not envisage the possibility of an action on structures at or near the ventral surface of the brain stem, reached after the drug had passed into the subarachnoid space through the lateral recesses. Recently the high potency of morphine in producing analgesia when introduced into the fourth ventricle was demonstrated in cats, but it was further noted that morphine was as effective when infused into the subarachnoid space beneath the ventral surface of the brain stem, although it did not enter any part of the ventricular system (Dey & Feldberg, 1975). It was therefore concluded that the analgesic effect of morphine when given by the intraventricular route, and in fact when given intravenously, also resulted from an action on structures situated near the ventral surface of the brain stem. Although this may be a main site of action, it is probably not the only one.

The importance of species differences is seen from the results obtained by Blane, Boura, Fitzgerald & Lister (1967) when they compared the analgesic action of subcutaneous injections of etorphine with that of morphine in different species. Etorphine was about 850 times more potent than morphine in mice, about 1700 times more potent in rats and about 8600 times more potent in guinea-pigs. In man the analgesic action of etorphine appears to be about 1000 times greater than that of morphine (Blane & Robbie, 1970) although no exact comparison has been made. A table compiled by Jaffe (1965) from various publications compares the relative analgesic potencies of pethidine and codeine on subcutaneous injection in man to that of morphine. The analgesic action of pethidine is given as an eighth to a tenth, and of codeine as a twelfth that of morphine. Apomorphine is not used clinically as an analgesic and data are not available for a quantitative comparison with morphine.

The importance of route of administration is seen from results obtained by von Cube, Teschenmacher, Herz & Hess (1970). They compared the antinociceptive action of etorphine and morphine in rabbits; when injected intravenously, etorphine was nearly 10,000 times as potent, but injected intraventricularly only about 70 times as potent as morphine. This ratio of about 70 to 1 is practically the same as that observed during the present experiments on cats for the hyperglycaemic action of etorphine and morphine infused into the fourth ventricle: the ratio was about 75 to 1. Thus it may well be that a comparison employing both the same route of administration and the same species would reveal a close correlation between the two activities of the analgesic drugs examined in the present paper.

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