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INVESTIGATIONS ON THE HYPOTENSIVE EFFECT OF THE HYDROGENATED ERGOT ALKALOIDS

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The effects of the hydrogenated alkaloids of ergot on the circulation are extremely complex. When administered intravenously to the anaesthetized intact cat, these agents produce a fall in blood pressure (Rothlin, 1946). This effect is mainly due to a central action. After section of the spinal cord at the level of the first cervical vertebra (C1) and destruction of the medulla oblongata (i.e., in the spinal cat) these alkaloids produce an increase in blood pressure (Rothlin, 1946). The rise is brought about by a direct constriction of those vessels which, having been deprived of tonic innervation from the vasomotor centre, are especially sensitive to vasoconstrictor stimuli. In isolated vessels, e.g., cattle artery strips *in vitro*, blood vessels of the rabbit ear or of frog extremities, the administration of the hydrogenated alkaloids of ergot causes vasoconstriction, although not regularly (Rothlin, 1946). However, if the sympathetic pathways from the vasomotor centre to the vessels are intact, the intra-arterial injection of these alkaloids to anaesthetized cats, and to unanaesthetized human beings, leads to vasodilatation and not to vasoconstriction (Bircher and Cerletti, 1949 ; Barcroft, Konzett, and Swan, 1951). This peripheral vasodilator effect is presumably associated with a blockade of adrenergic impulses, since under suitable conditions a fall in blood pressure can also be produced in the spinal cat ; i.e., if sympathetic tone is restored by a constant intravenous infusion of adrenaline or noradrenaline and a long-lasting increase in blood pressure produced, the hydrogenated alkaloids of ergot cause a fall of blood pressure (Rothlin, 1949).

Therefore the fall in blood pressure produced in the anaesthetized intact cat by the hydrogenated alkaloids of ergot is not exclusively due to a central action. A peripheral blockade of adrenergic impulses may also play a role.

After transection of the spinal cord above the sixth thoracic segment, the administration of dihydroergocornine causes a rise of blood pressure, whereas after transection below this level it causes a fall (Bluntschli, 1948). It therefore seems necessary to have an uninterrupted pathway from the medulla oblongata down to a certain spinal segment in order that the central effects of this alkaloid may be transmitted to the periphery.

The purpose of the present investigation was to locate more precisely the central site of hypotensive action of the hydrogenated ergot alkaloids, as well as to acquire further information on the nervous pathways conducting this effect to the periphery.

We therefore studied the effects of hydrogenated ergot alkaloids in the cat after transection of the spinal cord at the level of the first and seventh thoracic vertebra (T1 and T7), to supplement previous findings. Their effects were also investigated in the decerebrated cat, in which the higher centres of autonomic regulation in the diencephalon are absent but the medulla oblongata is intact. In some experiments transection of the spinal cord at the level of the sixth cervical vertebra (C6), the first (T1) and the seventh thoracic vertebra (T7) was carried out after decerebration.

Since the central effects of these alkaloids must be transmitted to the periphery by autonomic efferent fibres, it was of interest to observe how their actions were affected by the interruption of autonomic efferent pathways. For this purpose the autonomic synapses, in the anaesthetized intact cat and in the decerebrated cat, were blocked by the injection or infusion of tetraethylammonium. Similar experiments were carried out after transection of the spinal cord at the level of T1 and T7.

Finally, the effects of the hydrogenated ergot alkaloids were studied in the spinal cat, after the spinal cord had been cut at the level of T7. In some experiments the spinal cord was completely destroyed.

METHODS

The experiments were carried out on 115 cats weighing 2.1–4.1 kg. In the intact animal anaesthesia was produced by subcutaneous administration of a mixture of chloralose (0.05 g./kg.) and urethane (0.50

g./kg.). In experiments on the decerebrated cat or the spinal animal, ether anaesthesia was used only during the operation. Decerebration was carried out just above the posterior quadrigeminal bodies after ligation of both common carotid arteries. In some experiments the vagi were cut.

Blood pressure was registered by a mercury manometer connected to the left carotid artery. Records of the renal and intestinal volumes were taken to obtain information on the blood flow through these organs. Renal volume (left kidney) was recorded plethysmographically by means of Roy's oncometer. Intestinal volume was recorded by means of a glass oncometer.

Dihydroergocornine methanesulphonate or a mixture of the methanesulphonates of the three alkaloids dihydroergocornine, dihydroergocristine, and dihydroergokryptine in equal proportions (Hydergine), or dihydroergotamine methanesulphonate were injected into the jugular vein in doses of 0.03 mg./kg. and 0.1 mg./kg.

For purposes of comparison, ergotamine tartrate was injected in doses of 0.03 mg./kg. and 0.1 mg./kg. intravenously in 21 experiments.

Tetraethylammonium chloride was injected (two injections of 10 mg./kg. at an interval of 4–10 minutes) or infused for 20–30 minutes in a concentration of 1:1,000 (1–2 mg./min.) to provide ganglionic blockade.

In most experiments adrenaline and noradrenaline were injected intravenously before and after the administration of the ergot alkaloids. The inhibition of adrenaline and noradrenaline by the hydrogenated ergot alkaloids will not be described in the present paper.

Results

In the Anaesthetized Intact Cat

Transection of the Spinal Cord at T7.—Section of the spinal cord at T7 in the cat under chloralose urethane anaesthesia caused a fall of blood pressure. The average blood pressure in eight cats at the beginning of the experiment was 171 (±12) mm. Hg.* In 12 animals after section at T7 the average blood pressure was 125 (±15) mm. Hg. Thus transection of the spinal cord reduced the blood pressure by approximately 27%.

Although the blood pressure was reduced after transection of the cord at T7, dihydroergocornine or Hydergine (0.03 mg./kg.) caused a further fall of 26 (±2) mm. Hg (average) in blood pressure in all six experiments (see Fig. 1).

Renal volume decreased because of the fall in blood pressure. There was generally little change in the volume of the intestines, but in isolated experiments it increased.

Thus the effect of the hydrogenated ergot alkaloids in the anaesthetized cat after section at T7 was fundamentally the same as that in the anaesthetized intact animal (Rothlin, 1946).

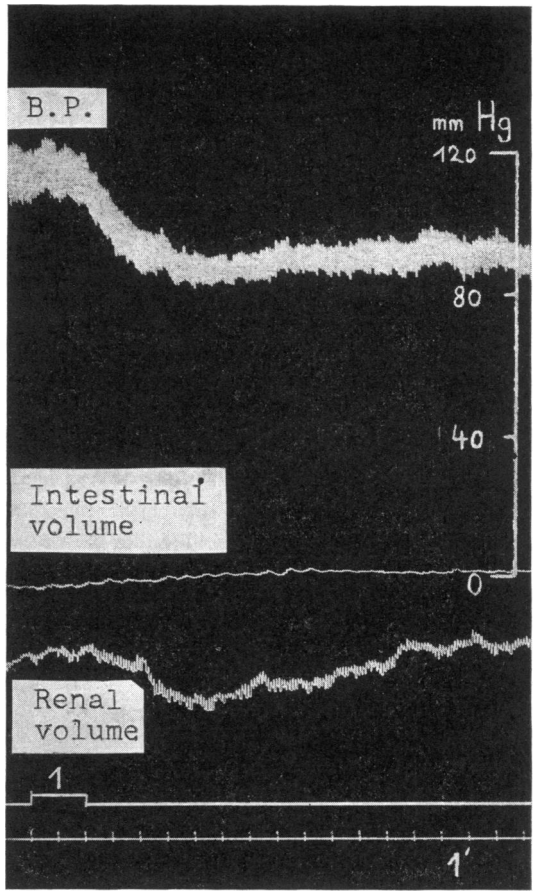

FIG. 1.—Hydergine reduces blood pressure in the cat after transection of the spinal cord at T7. Tracings from top to bottom are: blood pressure (mercury manometer connected to carotid artery), volume of the intestine and volume of the left kidney (plethysmography). Up-stroke=increase in volume, down-stroke=decrease in volume. Time in minutes. At 1, injection of 0.03 mg./kg. Hydergine.

Transection of the Spinal Cord at T1.—The average blood pressure in 26 animals after transection of the cord at T1 was 108 (±26) mm. Hg, i.e., approximately 63% of that in the intact animal and approximately 87% of that in the cat after transection at T7.

Doses of 0.03 and 0.1 mg./kg. dihydroergocornine and Hydergine had no uniform effect on blood pressure. In 10 experiments there was a fall (see Fig. 2*a*), in 7 there was a rise (see Fig. 2*b*), and in 5 there was no significant change.

There was no clear-cut relationship between the blood pressure values immediately before administration of the alkaloids and their effect on blood pressure.

* The figures in parentheses indicate standard deviation.

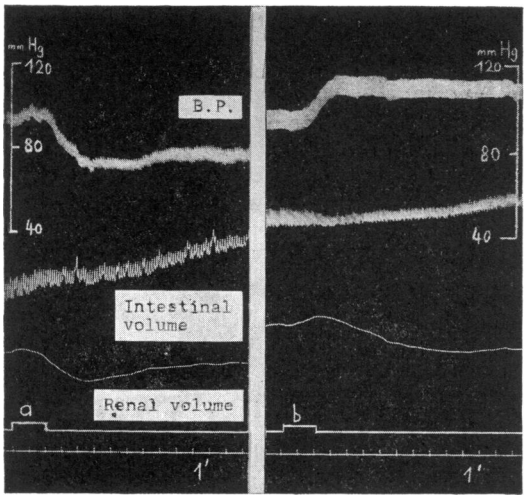

FIG. 2.—Effect of Hydergine and dihydroergocornine on blood pressure in two cats after transection of the spinal cord at T1. Tracings: from top to bottom as in Fig. 1. (*a*) Injection of 0.03 mg./kg. Hydergine. (*b*) Injection of 0.03 mg./kg. dihydroergocornine. See text.

Changes in renal volume were generally due to changes in blood pressure. There was very little change in the volume of the intestines.

In the Decerebrated Cat

The average blood pressure in 38 decerebrated cats was 126 (±17) mm. Hg. In 16 out of 17 experiments doses of 0.03 and 0.1 mg./kg. dihydroergocornine, Hydergine, and dihydroergotamine reduced the blood pressure (see Fig. 3). The average fall in blood pressure was 37 (±18) mm. Hg. In one experiment there was an increase in pressure.

The vascular reaction was principally the same as in the intact animal, i.e., the changes in renal volume were due to changes in blood pressure (see Fig. 3), and intestinal volume was only slightly affected.

Ergotamine, in contrast to the hydrogenated alkaloids, caused a rise of blood pressure in the decerebrated cat as in the anaesthetized intact animal.

Transection of the Spinal Cord at T7.—Transection of the spinal cord at T7 led to a decrease in blood pressure in the decerebrated cat as in the anaesthetized intact animal. The average blood pressure in 19 animals after transection of the cord was 96 (±21) mm. Hg, i.e., approximately 74% of that recorded before the operation.

The effects of 0.03 and 0.1 mg./kg. dihydroergocornine, Hydergine, and dihydroergotamine were studied in 14 experiments. In 11 cats the blood pressure fell by 22 (±14) mm. Hg (average), in one cat it rose, and in two cats there was no significant change. In the only experiment in which Hydergine (0.1 mg./kg.) produced a rise in pressure the initial blood pressure values were particularly low (66 mm. Hg). The vascular reaction

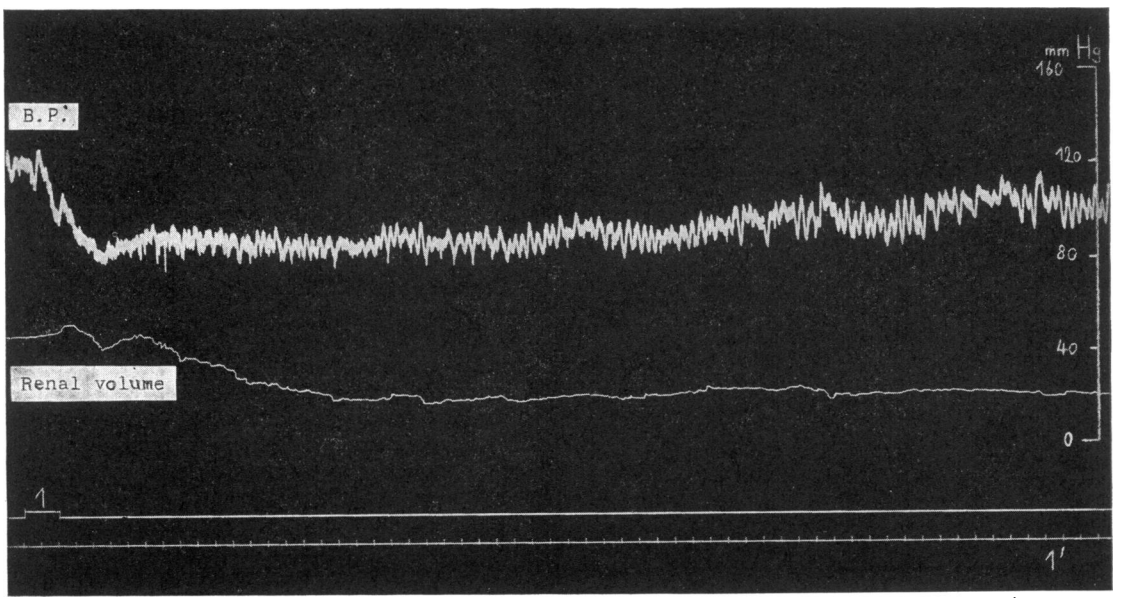

FIG. 3.—Dihydroergocornine reduces blood pressure in the decerebrated cat. Upper tracing: blood pressure. Lower tracing: volume of left kidney. Time in minutes. At 1, injection of 0.03 mg./kg. dihydroergocornine.

was identical with that in the decerebrated animal *not* subjected to transection of the spinal cord.

Ergotamine regularly increased blood pressure in the decerebrated cat both before and after transection of the spinal cord at T7.

Transection of the Spinal Cord at T1 and C6.—After decerebration and transection of the spinal cord at T1, the average blood pressure in 13 animals was 88 (±15) mm. Hg, i.e., approximately 70% of that after decerebration alone.

Doses of 0.03 and 0.1 mg./kg. dihydroergocornine, Hydergine, and dihydroergotamine given to nine animals had no uniform effect on the blood pressure. In three cats there was a decrease, and in six cats an increase. Changes in renal volume were due to changes in blood pressure.

Furthermore, after transection of the cord at C6 the hydrogenated ergot alkaloids exerted no uniform effect. In three experiments the blood pressure fell, in two experiments it rose, in one experiment it remained unchanged.

Ergotamine regularly produced an increase in blood pressure in the decerebrated cat after transection of the cord at T1.

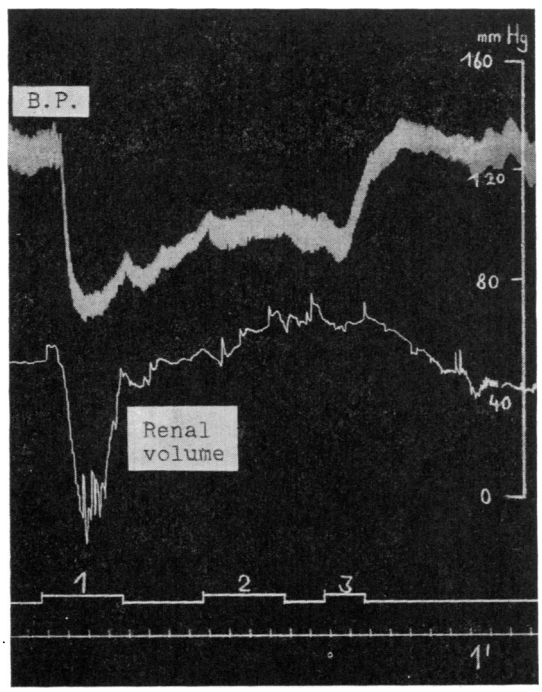

FIG. 4.—Dihydroergocornine increases blood pressure in the cat pre-treated with tetraethylammonium. Tracings from top to bottom as in Fig. 3. (1) Injection of 10 mg./kg. tetraethylammonium. (2) Injection of 10 mg./kg. tetraethylammonium. (3) Injection of 0.1 mg./kg. dihydroergocornine.

The Effect of Tetraethylammonium Chloride

The dose of tetraethylammonium employed by us (see Methods) blocks the majority of the autonomic synapses and thus prevents the transmission of stimuli from the centre to the periphery (Acheson and Moe, 1946; Moe and Freyburger, 1950).

The injection or infusion of tetraethylammonium produced a considerable fall in blood pressure in the anaesthetized intact and in the decerebrated animal. The injection of 0.03–0.1 mg./kg. dihydroergocornine, Hydergine, or dihydroergotamine after the injection or during the infusion of tetraethylammonium, i.e., when the blood pressure had reached a new level between 80 and 100 mm. Hg, generally caused a rise of blood pressure. In the intact animal the blood pressure rose in seven experiments (see Fig. 4) and fell in only one. After transection of the cord at T7 and administration of tetraethylammonium, the hydrogenated ergot alkaloids caused a rise of blood pressure (five experiments). Similarly, after transection of the cord at T1 and tetraethylammonium, the administration of these alkaloids led to an increase in blood pressure (four experiments).

In the decerebrated animal the blood pressure increased in six experiments and decreased in two.

In most of the animals treated with tetraethylammonium renal and intestinal volumes increased because of the rise in blood pressure. In some experiments they were reduced or showed no significant change.

The Spinal Cat after Transection or Destruction of the Spinal Cord

In the spinal animal the hydrogenated alkaloids of ergot always caused a rise of blood pressure after transection of the spinal cord at T7 or after complete destruction of the cord (see Fig. 5). Renal volume increased due to the rise in blood pressure.

DISCUSSION

The observations made show that the hydrogenated alkaloids of ergot, dihydroergocornine, Hydergine, and dihydroergotamine cause a fall of blood pressure provided that the medulla oblongata is intact and the spinal cord is intact as far down as the seventh thoracic segment (see Table I). The presence or absence of the diencephalon and cerebrum is not of importance, since a fall in blood pressure occurs in the decerebrated cat as well as in the anaesthetized intact animal. The primary importance of the medulla oblongata for the production of a fall of blood pressure is clearly shown in the experiments on the decerebrated cat. Thus, the diencephalon, in which Hess (1947) located

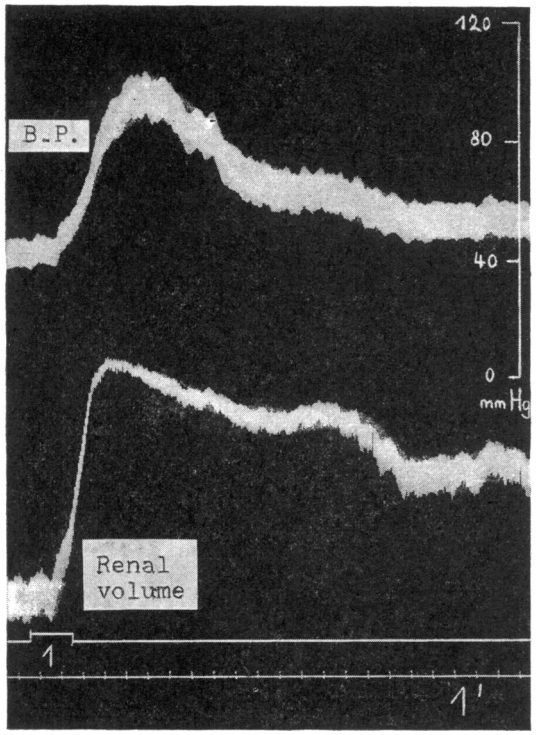

FIG. 5.—Hydergine increases blood pressure in the spinal cat after destruction of the cord. Tracings from top to bottom as in Fig. 3. At 1, injection of 0.03 mg./kg. Hydergine.

areas responsible for a syndrome accompanied by a fall in blood pressure, seems to play no significant role in the production of the hypotensive effect of the hydrogenated ergot alkaloids.

After the connection between the medulla oblongata and the spinal cord is broken at the level of the sixth cervical or the first thoracic vertebra, the hydrogenated alkaloids of ergot do not regularly produce a fall in blood pressure; there may be an increase (see Table I) or no significant change. Thus our observations are not in complete accord with those of Bluntschli (1948), who reported that, after transection of the spinal cord at the level of the first thoracic segment, dihydroergocornine regularly caused an increase in blood pressure. The fact that we carried out a greater number of experiments may account for the differences between Bluntschli's findings and ours.

In any case, the effects of the hydrogenated alkaloids of ergot in the decerebrated cat after transection of the cord at T1 are similar to those in the anaesthetized intact animal after transection of the cord at the same level. In some experiments the blood pressure fell, in others it rose (see Table I).

It seems that when the spinal cord is transected at C6 or T1 some of the neural pathways which transmit the central hypotensive impulses to the periphery are interrupted and put out of action before they leave the spinal cord. If this is so, the direct vasoconstrictor effect of the hydrogenated ergot alkaloids may become predominant in some experiments and cause the blood pressure to rise.

Taylor and Page (1951) report that adrenaline and noradrenaline behave similarly. The injection of adrenaline or noradrenaline into the isolated perfused brain produces a fall in blood pressure throughout the general circulation if the spinal cord is intact but not if it has been cut at C6.

The direct vascular effect of the hydrogenated alkaloids of ergot is particularly impressive in the spinal cat (Rothlin, 1946). An increase in blood pressure is always observed in the spinal cat whether the spinal cord is intact, has been transected at T1, or completely removed (see Table I).

Which neural pathways remain for the transmission of central hypotensive impulses after transection of the cord at the level of the sixth cervical or the first thoracic vertebra? A bradycardia can be transmitted via the vagus, causing cardiac output to be reduced and blood pressure to fall (Rothlin, 1946). However, after bilateral

TABLE I

THE EFFECT ON BLOOD PRESSURE OF DIHYDROERGOCORNINE, HYDERGINE, AND DIHYDROERGOTAMINE IN DOSES OF 0.03 MG./KG. AND 0.1 MG./KG.

The figures indicate the number of experiments

Test Object	Blood Pressure		
	Fall	Rise	Unchanged
Anaesthetized intact cat after section of spinal cord at T1 ..	10	7	5
Anaesthetized intact cat after section of spinal cord at T7 ..	6	—	—
Decerebrated cat	16	1	—
Decerebrated cat after section of spinal cord at C6	3	2	1
Decerebrated cat after section of spinal cord at T1	3	6	—
Decerebrated cat after section of spinal cord at T7	11	1	2
Anaesthetized intact cat after pretreatment with tetraethylammonium	1	7	—
Anaesthetized intact cat after pretreatment with tetraethylammonium and section of spinal cord at T1	—	4	—
Anaesthetized intact cat after pretreatment with tetraethylammonium and section of spinal cord at T7	—	5	—
Decerebrated cat after pre-treatment with tetraethylammonium	2	6	—
Spinal cat after section of cord at T7	—	5	—
Spinal cat after destruction of cord	—	9	—

section of the vagi the hydrogenated alkaloids of ergot may still cause a fall of blood pressure. It is possible that the parasympathetic vasodilator nerves which originate in the medulla oblongata or the pons, such as are to be found in the chorda tympani, the nervus petrosus minor, and the nervus lingualis, play a role. Stimulation of these nerves liberates acetylcholine and may cause dilatation of the vessels of the salivary glands and tongue, as well as a fall in blood pressure (Feldberg, 1933).

The fact that the hydrogenated alkaloids of ergot caused a fall of blood pressure in only half of the experiments after transection of the cord at T1 in the intact cat as well as in the decerebrated animal, but in all experiments after transection of the cord at T7, suggests that there are neural pathways which leave the spinal cord between T1 and T7 and transmit the efferent hypotensive impulses to the organs in the periphery. The nerves concerned are most probably the sympathetic nerve fibres which transmit both vasoconstrictor and vasodilator impulses from the vasomotor centres to the periphery (Folkow and Uvnäs, 1948).

According to prevailing anatomical concepts no impulses from higher centres can be transmitted via sympathetic nerves to the peripheral organs after transection of the cord at C6 or T1, because the highest sympathetic preganglionic fibres in the cat leave the spinal cord at T1 or T2 (Fulton, 1943). However, after section of the cord at T7 the sympathetic preganglionic fibres which emerge above T7 can reach their effector organs in the head, the neck, the arms, the thorax (including the heart and the lungs), and certain portions of the abdomen. If the central effects of the hydrogenated ergot alkaloids are transmitted to the above-mentioned effector organs via the sympathetic nerves, the blood pressure falls. This does not exclude the probability that the organs supplied with sympathetic nerves from below T7 are also involved in the fall of blood pressure caused by these substances in the anaesthetized intact cat.

It has not yet been conclusively established whether the hydrogenated alkaloids of ergot depress the outflow of vasoconstrictor impulses from the vasomotor centre or whether they enhance the outflow of vasodilator impulses from the vasodilator centre, or whether both these mechanisms are involved.

In view of the fact that the hydrogenated alkaloids of ergot can exert a central inhibition of baroceptive reflexes (Rothlin, 1946; Sutton, Cerletti, and Taeschler, 1950), prevent central fluctuations in blood pressure (Rothlin and Cerletti, 1949), and potentiate the effects of analgesics (David and Semler, 1952), it is not improbable that they inhibit vasoconstrictor impulses centrally.

Further evidence that the fall of blood pressure caused by the hydrogenated alkaloids is of central origin and is transmitted to the periphery by autonomic pathways is provided by the observation that after tetraethylammonium the hydrogenated alkaloids of ergot cause a rise of blood pressure. Whereas tetraethylammonium intensifies the effects on blood pressure of substances with a peripheral site of action, such as histamine and mecholyl (Page and Taylor, 1950), it reverses the effects of the hydrogenated alkaloids of ergot, so that blood pressure rises instead of falling. This difference between the hydrogenated ergot alkaloids and vasodilator substances with a peripheral site of action is strong evidence that the fall of blood pressure caused by these alkaloids is predominantly of central origin. Their effect on blood pressure in the anaesthetized intact or decerebrated cat after chemical blockade of the autonomic efferent pathways is similar to that in the spinal animal. In the spinal animal the alkaloids increase the blood pressure because the destruction of the medulla oblongata prevents a central hypotensive action, and, consequently, the direct vasoconstrictor action predominates. After chemical blockade of the peripheral autonomic synapses the hydrogenated ergot alkaloids cause a rise of blood pressure because the transmission of the central hypotensive impulses through the sympathetic nerves is interrupted in the synapses and, consequently, the normally latent direct vasoconstrictor action predominates.

Therefore, the medulla oblongata is the main central site of hypotensive action of the hydrogenated ergot alkaloids, and the upper sympathetic fibres (down to T7) transmit the central impulses to the periphery.

SUMMARY

1. The hydrogenated alkaloids of ergot, dihydroergocornine, Hydergine (a mixture of equal parts of dihydroergocornine, dihydroergokryptine, and dihydroergocristine), and dihydroergotamine caused a fall of blood pressure in the anaesthetized intact cat and in the decerebrated cat, mainly by an action on the vasomotor centres in the medulla oblongata.

2. After section of the spinal cord at the level of the seventh thoracic vertebra, these substances regularly caused a fall in blood pressure in the anaesthetized intact cat and in the decerebrated animal.

3. After section of the spinal cord at the level of the sixth cervical or the first thoracic vertebra, these alkaloids did not regularly produce a fall in blood pressure in the anaesthetized intact cat and the decerebrated animal; in approximately half the experiments an increase in blood pressure was observed.

4. After ganglionic blockade by means of tetraethylammonium the hydrogenated alkaloids of ergot generally produced an increase in blood pressure in the anaesthetized intact cat and in the decerebrated cat.

5. An increase in blood pressure was always produced by the alkaloids in the spinal cat, even after section of the cord at the level of the seventh thoracic vertebra or after complete destruction of the cord.

6. Therefore, *the vasomotor centres, as the main site of action,* and *the upper part of the sympathetic outflow, as pathways conducting the impulses,* have to be intact for the hydrogenated alkaloids of ergot to cause a fall of blood pressure. When the vasomotor centres or the autonomic efferent fibres are put out of action, the normally latent vasoconstrictor effect of these alkaloids may predominate and produce an increase in blood pressure.

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