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THE ACTION OF ERGOTAMINE ON THE INTRACRANIAL VENOUS PRESSURE AND ON THE CEREBRAL VENOUS OUTFLOW OF THE DOG

BY

A. CARPI AND M. VIRNO

From the Department of Therapeutic Chemistry, Istituto Superiore di Sanità, Rome, Italy

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The effect of ergotamine and dihydroergotamine on the cerebral circulation was studied in the dog, anaesthetized with chloralose, by recording the intracranial venous pressure and the venous outflow from the superior cerebral vein. Under optimal experimental conditions, ergotamine (5 to 10 μg./kg.) and dihydroergotamine (100 μg./kg.) gave a marked and long-lasting cerebral vasoconstriction accompanied by a slight hypertension. The cerebral vasoconstriction provoked by ergotamine may be very small and was sometimes absent when the cerebral blood-flow was low. This vasoconstrictor effect is more pronounced the higher the initial intracranial venous pressure and hence the cerebral blood-flow. After the induction of a cerebral vasodilatation by 48/80 or strychnine, the vasoconstrictor action of ergotamine was more pronounced. The effect was not observed when CO_2 was employed to modify the intracranial venous pressure. Simultaneous registration of the cerebral, nasal cavity, and kidney vascular responses demonstrated the relative specificity of the action of ergotamine on the cerebral vessels. The small doses of ergotamine used may weaken or abolish the vasoconstrictor action of adrenaline on cerebral vessels. The modification of the responses of the cerebral circulation which such factors as anaesthesia, respiratory acidosis, and operative trauma can produce have been confirmed and emphasized. The results support the view that the vasoconstrictor action of ergotamine on the cerebral vessels might account for the therapeutic value of this drug in migraine.

Although the efficacy of ergotamine in the treatment of migraine has been well known for a long time (Thomson, 1894; Maier, 1926; Tzanck, 1928; Lennox, 1934), the mechanism of its action is still a subject for discussion. The suggestion, based upon clinical observations, that ergotamine exerts its therapeutic effect through a vasoconstrictor action on the cranial vessels (Lennox and von Storch, 1936; Graham and Wolff, 1938; Wolff, 1948) has hitherto received little experimental confirmation. Systematic investigations carried out in animals and men have very rarely demonstrated a clear cerebral vasoconstrictor action of ergotamine even when large doses were administered.

The direct observation of pial vessels (Ley and de la Fontaine-Verwey, 1929; Pool and Nason, 1935), tissue thermometry (Lubsen, 1940; Schmidt, 1934), perfusion methods (Heymans and Regniers, 1927), blood flow measurements in the internal carotid artery (Schneider and Schneider, 1934b; Dumke and Schmidt, 1943), plethysmographic techniques, registration of cerebrospinal fluid pressure (Koopmans, 1939; Lennox, Gibbs and Gibbs, 1935; Cannavà and Musmeci, 1940) and the nitrous oxide method (Abreu, Liddle, Handley, and Elliot, 1947; Abreu, Liddle, Burks, Simon, Sutherland, and Gordan, 1948) applied to various animal species and to man (Lennox *et al.*, 1935; Abreu *et al.*, 1948) have never shown a clear-cut vasoconstrictor action of ergotamine. Such effects sometimes followed substantial doses (0.05 to 1.0 mg./kg.) or intracarotid injection (Dumke and Schmidt, 1943; Schneider and Schneider, 1934b; Koopmans, 1939; Ley and de la Fontaine-Verwey, 1929; Pool and Nason, 1935). Heymans and Regniers (1927), Schmidt (1934), Lennox *et al.* (1935), Cannavà and Musmeci (1940), Lubsen (1940), and Abreu *et al.* (1947, 1948) reported that ergotamine caused a rise of the cerebral blood-flow which according to Lennox *et al.* (1935), depended on the arterial hypertensive action of the alkaloid.

Previous observations made in this laboratory on the registration of the cerebral venous pressure through the various branches of the external jugular vein in the dog anaesthetized with chloralose have confirmed that this method enables the cerebral vasomotor effect of various drugs to be studied (Bovet, Gatti and Virno, 1955a and b; Virno, Gertner, and Bovet, 1956; Bovet, Virno, Gatti, and Carpi, 1957). The object of the present study was to obtain further information on the vasomotor effect of ergotamine on the cerebral circulation. In order to obtain a closer parallel between clinical and laboratory observations, care was taken to observe the effect of minimal doses. The experiments were carried out both under normal conditions and in animals previously treated with cerebral vasodilator agents.

METHODS

In the dog anaesthetized with chloralose (120 mg./kg., i.v.) the peripheral venous pressure was registered by means of a polyvinyl catheter introduced into the external jugular vein and manipulated by way of the internal maxillary and the superior cerebral veins until it reached as near as possible to the orifice of the temporal foramen. Nasal cavity volume was recorded according to the method of François-Frank (1894), modified in some details (Bovet *et al.*, 1957), and the renal volume was registered plethysmographically by means of Roy's oncometer. In some experiments, records of systemic venous pressures were registered by means of a catheter introduced through the external jugular vein into the superior vena cava.

For all these recordings water-manometers were employed, and the changes in the height of the column of water were recorded photographically according to the method of Baldes and Corbeile (1929) modified by Condorelli (1941).

In other experiments, the peripheral jugular pressure and the outflow from the superior cerebral vein were simultaneously registered. A second polyvinyl catheter was introduced into the opposite external jugular vein and manipulated, as previously described, towards the orifice of the temporal foramen. This catheter was used for recording the venous outflow and its free orifice was fixed on the same level as the external jugular vein. It was so arranged that the drops of blood short-circuited a pair of contacts connected through an electronic relay with a Fleisch's summator which automatically returned to zero every 15 sec. The blood was then recirculated into the external jugular vein at the same rate as the outflow. Blood clotting was prevented by the use of 10 mg./kg. of X50 (Geigy Ltd.). The exact position of the catheters was always verified by a dissection at the end of the experiments. Femoral blood pressure was recorded with a Ludwig's mercury-manometer.

Respiratory acidosis was induced by two different methods. In the first experimental group, the dog was allowed to breathe gas mixtures containing 10 to 30% CO_2 in air. The second group of animals were given gallamine in a sufficient quantity to paralyse the skeletal musculature and were given artificial respiration. Hypercapnia was obtained here by reducing the minute volume to approximately 1/5 of the normal value. Air was in this case substituted by oxygen to avoid anoxemia and the arterial blood *p*H was repeatedly measured by means of a glass-electrode.

All drugs were administered into the saphenous vein.

RESULTS

Effect of Ergotamine on the Cerebral Vessels and the other Vascular Areas under Normal Conditions.—When 5 to 10 μg./kg. of ergotamine was administered to an animal it was observed that, besides the well-known rise in arterial pressure (10 to 20 mm. Hg), a significant fall in the cephalic venous pressure occurred; the initial level of 15 to 20 cm. H_2O fell to 8 to 12 cm. H_2O, remaining at this pressure for many hours (Fig. 1). Under these experimental conditions, after ergotamine, the peripheral jugular pressure did not return to its original level even after a period of 4 hr. This effect is less pronounced if the peripheral pressure is already low before the ergotamine administration (Fig. 6).

In 10 animals, the average fall of cephalic venous pressure provoked by 5 to 10 μg./kg. of ergotamine was 3.5 cm. H_2O (1.5 to 7.0 cm. H_2O). Compared with the action of adrenaline (1 to 3 μg./kg.) this effect of ergotamine was more intense in 3, equal in 4 and weaker in 1 of eight experiments undertaken. Compared with the long-lasting action of ergotamine, the effect of adrenaline on the peripheral jugular pressure lasted no more than 2 to 4 min.

Repeated injections of the alkaloid do not give rise to a further lowering of the cephalic venous pressure. Very often a slight increase in the peripheral jugular pressure together with a marked rise of arterial pressure was observed, especially if larger doses of the drug were injected. This was only partially related to the low level of the peripheral jugular pressure after the first administration of the drug.

The outflow from the superior cerebral vein was decreased by ergotamine and this reduction ran strictly parallel to the fall in the peripheral jugular pressure. For example in one experiment it was observed that a fall from 15 to 11.5 cm. H_2O in the cephalic venous pressure corresponded to a 30% decrease in the venous outflow of the opposite side.

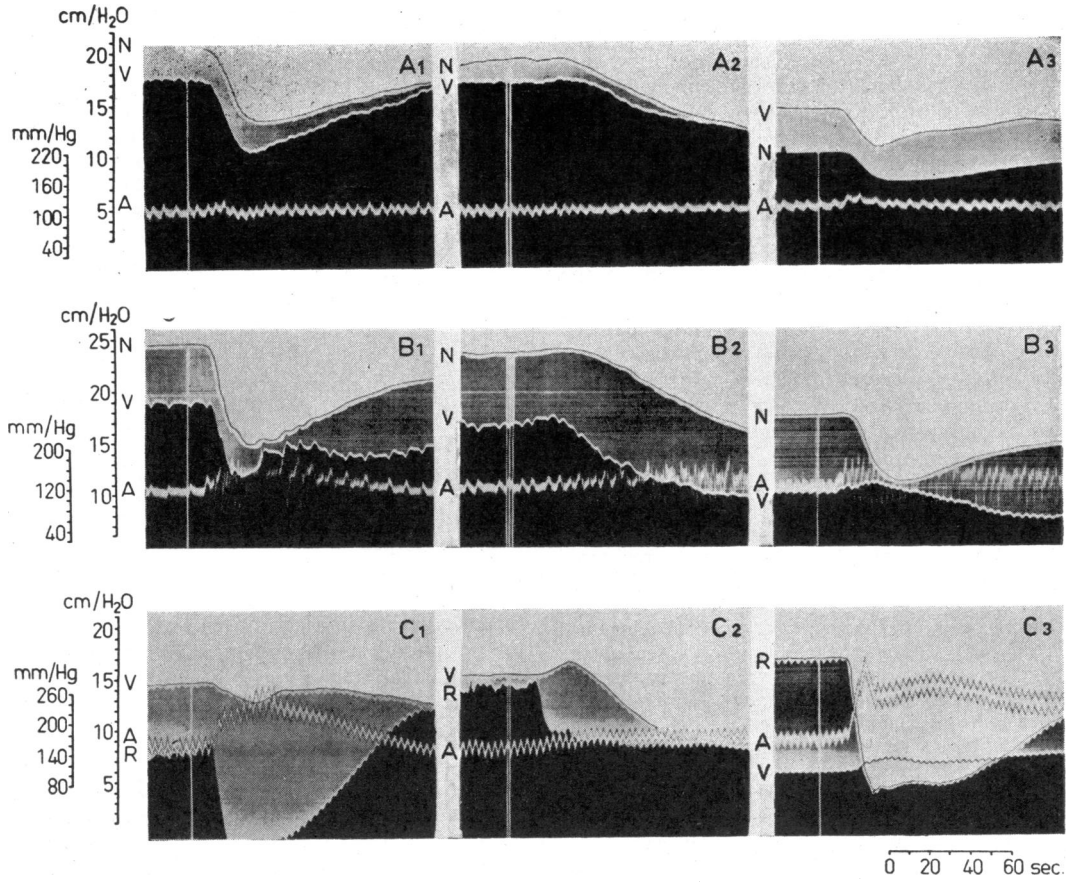

FIG. 1.—Effect of small doses of ergotamine on the cephalic venous pressure, on the nasal and the renal plethysmogram and its antagonism to the action of adrenaline. In all tracings A = pressure in the femoral artery (mm. Hg); V = peripheral pressure in the internal maxillary vein (cm. H_2O); N = nasal cavity plethysmogram; R = renal plethysmogram. A_1, A_2, and A_3, male dog 14 kg. (21/6/56), chloralose anaesthesia; A_1, adrenaline 0.1 μg./kg.; A_2, ergotamine 5.0 μg./kg.; A_3, adrenaline 0.1 μg./kg. B_1, B_2, and B_3, male dog 18 kg. (13/6/56), chloralose anaesthesia; B_1, adrenaline 1 μg./kg.; B_2, ergotamine 10 μg./kg.; B_3, adrenaline 1 μg./kg. C_1, C_2, and C_3, male dog 16 kg. (24/7/56), chloralose anaesthesia; C_1, adrenaline 1 μg./kg.; C_2, ergotamine 10 μg./kg.; C_3, adrenaline 1 μg./kg.

The doses of ergotamine which lowered the cranial venous pressure also caused a constriction of the nasal vessels which corresponded to an increase in the total volume within the nasal cavity. Consequently a fall of the water column in the manometer connected to the closed nasal cavity was observed (Fig. 1, A_1, A_2, A_3, B_1, B_2, and B_3). In a series of 15 experiments it was observed that this vasoconstrictor effect on nasal vessels lasted in 7 cases more than 2 hr., whereas in the other 8 it disappeared 30 to 45 min. after the ergotamine injection. The intensity of the nasal vasoconstriction provoked by 5 to 10 μg./kg. of ergotamine was similar to that produced by 1 μg./kg. of adrenaline in 5 of 8 animals and less in the other 3. Ergotamine in the usual dose of 5 to 10 μg./kg. caused a slight and transient fall in the kidney volume which was always less than that provoked by 1 μg./kg. of adrenaline (Fig. 1, C_1, C_2, and C_3). The alkaloid had only a slight effect on the systemic venous pressure; a rise of 1 to 2 cm. H_2O after administration of 5 to 10 μg./kg. i.v. ergotamine was observed.

Influence of Ergotamine on the Cerebral Vascular Action of Adrenaline. — With the small doses used (5 to 10 μg./kg.), ergotamine did not clearly modify the arterial hypertension provoked by 0.1 to 3 μg./kg. of adrenaline (Fig. 1). Sometimes this action was slightly potentiated as previously observed by Hartman (1915), Woods, Nelson, and Nelson (1932), Herwick, Linegar and Koppanyi (1939), and Von Euler and Schmiterlöw (1944). The renal vasoconstrictor response to adrenaline was unaltered after ergotamine, and the

nasal vasoconstriction only partially reduced (Fig. 1). On the other hand the action of adrenaline on the cephalic venous pressure was clearly modified and closely related to the level of the peripheral jugular pressure at the moment of the injection of the hormone. In all cases where the injection of ergotamine produced a fall in the venous pressure which was equal to or more pronounced than that provoked by adrenaline, the further injection of adrenaline did not produce an additional fall in the cephalic venous pressure (Fig. 1, B_1, B_2, B_3, C_1, C_2, and C_3). However, if the jugular venous pressure after the injection of ergotamine did not fall to the level produced by adrenaline in the normal animal then a further injection of adrenaline might produce a further fall of the cephalic venous pressure (Fig. 1, A_1, A_2, and A_3). After doses of ergotamine (0.5 to 1 mg./kg.) large enough to produce anti-adrenaline actions, the typical adrenaline reversal reaction on the arterial blood pressure was observed; in this case the venous pressure followed passively the fall of the arterial pressure provoked by adrenaline.

Effects of Dihydroergotamine on the Cerebral Vessels and on the Cerebral Vascular Action of Adrenaline.—Dihydroergotamine in doses of 100 μg./kg. has a similar action on the peripheral jugular pressure and on the cerebral venous outflow as 5 to 10 μg./kg. of ergotamine. After such doses of dihydroergotamine, the action of adrenaline (1 to 3 μg./kg.) on the cephalic venous pressure was the more reduced the greater the fall in the peripheral jugular pressure provoked by the alkaloid.

Interaction Between the Vasoconstrictor Effect of Ergotamine and the Action of Some Cerebral Vasodilators.—From the results described, it was clear that ergotamine caused a fall in the peripheral jugular pressure which was more pronounced the higher the cephalic venous pressure before the administration of the alkaloid. Hence the action of ergotamine after the induction of a cerebral vasodilatation which produced a marked rise in cephalic venous pressure was studied. The histamine liberator 48/80, strychnine, and gas mixtures with high content of CO_2 were used, and the effect of ergotamine on the action of these vasodilator agents was investigated.

Compound 48/80 caused a marked and long-lasting rise in the peripheral jugular pressure. Under these conditions 5 to 10 μg./kg. of ergotamine significantly reduced the cephalic venous pressure to a level which was lower than that prior to the administration of the histamine-liberator. Consequently the injection of 48/80 before ergotamine gave rise to a more substantial effect of the

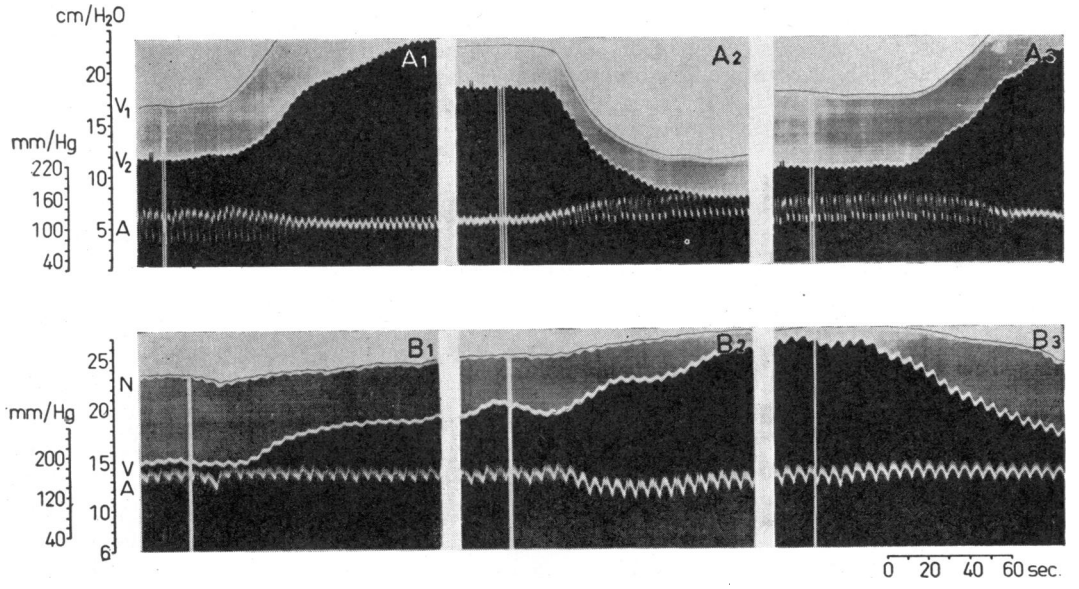

FIG. 2.—Interaction between 48/80 and ergotamine on the cephalic venous pressure and the nasal vessels. A_1, A_2, and A_3, male dog 14 kg. (1/7/55), chloralose anaesthesia. A=pressure in the femoral artery (mm. Hg); V_1=peripheral pressure in the external maxillary vein (cm. H_2O); V_2=peripheral pressure in the internal maxillary vein (cm. H_2O). A_1, 48/80 25 μg./kg.; A_2, ergotamine 10 μg./kg.; A_3, 48/80 50 μg./kg. B_1, B_2, and B_3, male dog 11 kg. (3/7/56), chloralose anaesthesia. A=pressure in the femoral artery (mm. Hg); V=peripheral pressure in the internal maxillary vein (cm. H_2O); N=nasal cavity plethysmogram. B_1, 48/80 25 μg./kg.; B_2, 48/80 25 μg./kg.; B_3, ergotamine 10 μg./kg.

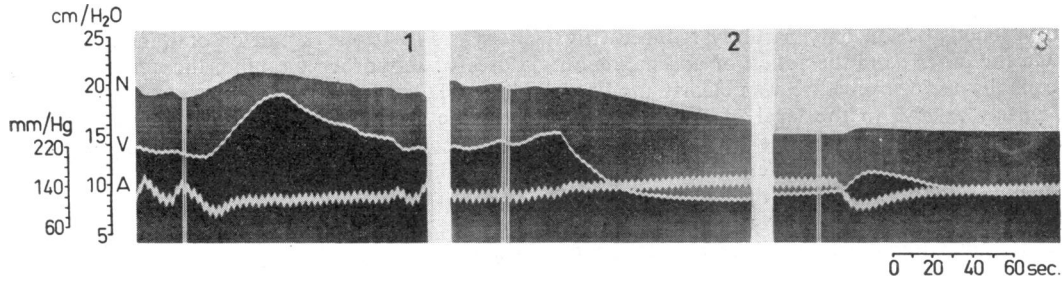

FIG. 3.—Action of histamine on the cephalic venous pressure, the nasal plethysmogram and its antagonism by ergotamine. Recordings as in Fig. 1. Female dog 14 kg. (25/5/56), chloralose anaesthesia. 1, histamine 1 μg./kg.; 2, ergotamine 10 μg./kg.; 3, histamine 1 μg./kg. i.v.

alkaloid (Fig. 2). In four experiments, the average fall of the peripheral jugular pressure caused by the alkaloid was 11.5 cm. H_2O (10.5 to 14.5 cm. H_2O). On the nasal vessels, the long-lasting vasodilator action of 48/80 is also evident without any marked change in the vasoconstrictor action of ergotamine being observed (Fig. 2, B_1, B_2, and B_3).

As repeated injections of 48/80 do not provoke constant vascular effects, it was difficult to obtain precise information about the influence of ergotamine on the action of the histamine-liberator; in only three such experiments a typical action of 48/80 in large doses on the peripheral jugular pressure was observed (Fig. 2, A_1, A_2, and A_3).

As previous experiments (Virno *et al.*, 1956) showed that histamine administered in doses of 0.5 to 1 μg./kg. gave a marked but brief rise of the cephalic venous pressure, a comparison was made of the effect of histamine itself before and after ergotamine injections. It was found that ergotamine (5 to 10 μg./kg.) moderately reduced the vasodilator action of histamine in 9 of 12 experiments (Fig. 3).

In anaesthetized dogs, which had received a dose of gallamine (2 to 4 mg./kg.) and were respired artificially, an intravenous injection of 100 to 500 μg./kg. of strychnine gave a slow but long-lasting rise in the cephalic venous pressure and an increase in the outflow of the superior cerebral vein. This effect was often coupled with some rise in arterial pressure (20 to 50 mm. Hg). Under these conditions, ergotamine caused a reduction in the peripheral jugular pressure and in the cerebral venous outflow to a level lower than that observed before strychnine (Fig. 4A). In nine experiments, the average fall of cephalic venous pressure caused by ergotamine (5 to 10 μg./kg.) was 7.0 cm. H_2O (3.5 to 12.0 cm. H_2O). Dihydroergotamine had the same effect (Fig. 4, B_1, B_2, and B_3). Strychnine did not give uniform results on the nasal cavity vessels: thus in one dog there was vasodilatation, in another vasoconstriction, whereas in

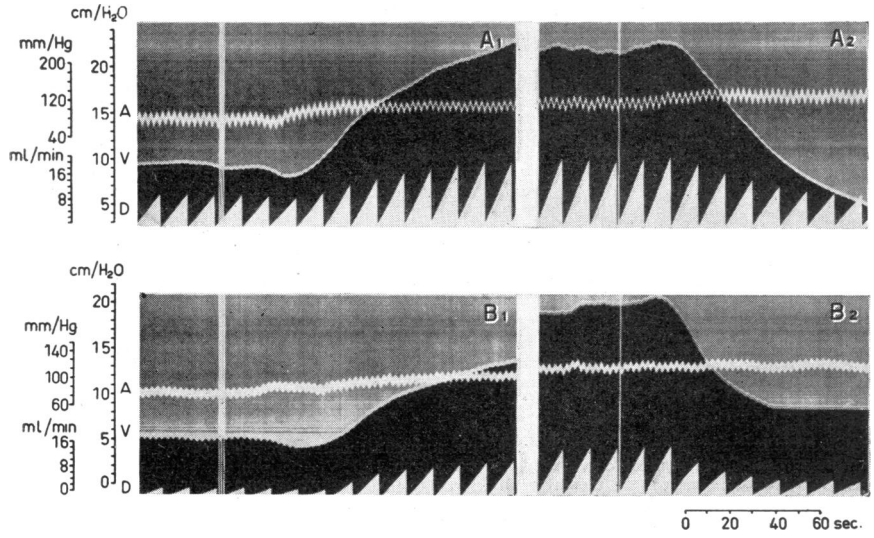

FIG. 4.—Influence of strychnine on the action of ergotamine and dihydroergotamine on the cephalic venous pressure and on the outflow from the superior cerebral vein. A and V as in Fig. 1. D=outflow from the left superior cerebral vein (ml./min.). A_1 and A_2, male dog 16 kg. (16/10/56), chloralose anaesthesia. A_1, strychnine 0.5 mg./kg.; A_2, ergotamine 10.0 μg./kg. B_1 and B_2, male dog 8 kg. (8/10/56), chloralose anaesthesia. B_1, strychnine 0.5 mg./kg.; B_2, dihydroergotamine 0.1 mg./kg. Both animals were maintained under artificial respiration after gallamine (4 mg./kg.).

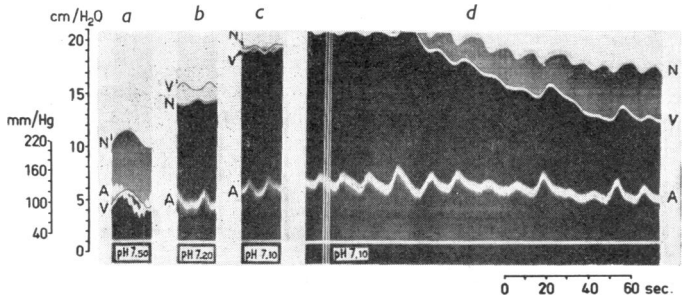

FIG. 5.—Influence of respiratory acidosis on the action of ergotamine on the cephalic venous pressure and on the nasal plethysmogram. Records as Fig. 1. The *p*H was determined from samples of the femoral arterial blood. Male dog 19 kg. (13/3/56) under chloralose anaesthesia after gallamine (1 mg./kg.). *a*, *p*H 7.5, artificial respiration with 2.5 l./min. O_2. *b*, *p*H 7.2, after 15 min. of artificial respiration with 0.45 l./min. O_2. *c*, *p*H 7.1, after 30 min. of artificial respiration with 0.45 l./min. O_2. *d*, *p*H 7.1, after 35 min. of artificial respiration with 0.45 l./min. O_2. At the three vertical lines ergotamine (10 μg./kg.) was injected.

three no change was observed. The vasoconstrictor effect of ergotamine on the nasal vessels in these experiments was the same as under normal conditions.

Because of the long-lasting action of strychnine, it was difficult to compare in the same dog the action of the drug before and after ergotamine. However, in 14 of the dogs, the administration of 500 μg./kg. of strychnine was clearly devoid of any effect on the arterial and on the peripheral jugular pressure 20 to 30 min. after the injection of 10 μg./kg. of ergotamine. Only in two other dogs did strychnine, administered 2 hr. after ergotamine, give a moderate vascular effect. It was also observed that 48/80 and histamine were still active in dogs which, after the administration of ergotamine, did not respond to strychnine.

Respiratory acidosis was induced in one series of experiments with dogs, which had received gallamine and which were maintained by artificial respiration, by a reduction of the minute volume to 1/5th of the normal value, oxygen being substituted for air, and in another series of dogs under normal respiration by the administration of gas mixtures containing 10 to 30% CO_2 in air. Hypercapnia caused a marked rise in the peripheral jugular pressure which could not be completely abolished by ergotamine (Fig. 5).

In six experiments, the fall in the cephalic venous pressure produced by ergotamine was, on an average, 4.5 cm. H_2O (3.5 to 7.0 cm. H_2O) and generally lasted up to 15 min. The vasodilator action of CO_2 on the nasal vessels was evident in 4 of the 6 experiments and was often preceded by a brief vasoconstrictor reaction; vasoconstriction after ergotamine was always weaker in these animals than under normal conditions (Fig. 5) and in 2 cases it was practically absent.

In some experiments the effect of ergotamine on the vascular reactions induced by respiratory acidosis was studied. Hypercapnia was obtained by administration of gas mixtures containing 40 to 50% CO_2 in O_2 during 10 or 20 respiratory cycles. Under these conditions there was a marked rise in the cerebral venous pressure which lasted 9 to 10 min., and a biphasic reaction of the nasal vessels which first constricted and then dilated with slight and inconsistent changes in arterial blood pressure.

Ergotamine in the usual dose of 5 to 10 μg./kg. weakened the effect of hypercapnia on the cephalic venous pressure and even more markedly on the nasal vessels (Fig. 6). It was also observed that, after ergotamine, hypercapnia caused a fall in the arterial pressure as previously described by Heymans and Bouckaert (1933). This fall in systemic pressure was transient and could not have interfered significantly with the reaction of the peripheral jugular pressure (Fig. 6).

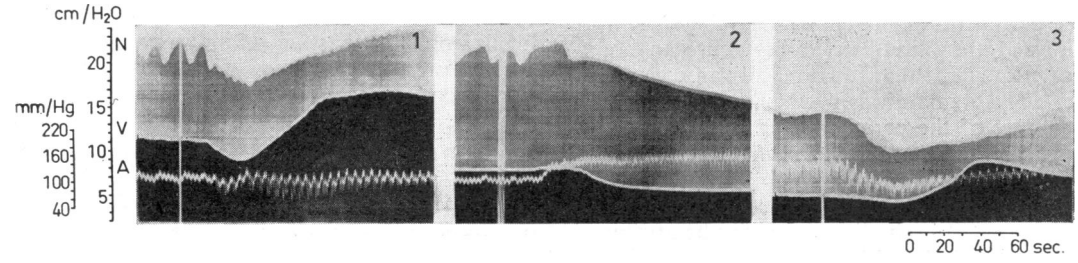

FIG. 6.—Effect of short-lasting hypercapnia on the cephalic venous pressure and nasal plethysmogram, and its antagonism by ergotamine. Records as in Fig. 1. Female dog 19 kg. (15/3/56), chloralose anaesthesia. 1, administration of a gas mixture containing 50% CO_2 in O_2 during 10 respirations. 2, ergotamine (10 μg./kg.). 3, administration of the same gas mixture during 10 respirations.

Discussion

The experiments reported here confirm that changes in the cerebral venous pressure as measured by means of a catheter introduced into the peripheral portion of the external jugular vein may be considered of significance in the study of the cerebral vascular reactions produced by the administration of various drugs. The fact that the arterial and peripheral jugular pressures may vary independently and often in opposite directions (Bovet *et al.*, 1955a and b ; Virno *et al.*, 1956 ; Bovet *et al.*, 1957) was confirmed and interpreted as demonstrating a direct effect of drugs on the peripheral resistance of the brain vessels. Under various experimental conditions, quite different reactions were noted on the cerebral, extracerebral and visceral circulation.

The conclusions drawn from these observations on venous pressure receive further support by experiments carried out on cerebral venous outflow ; generally a fall in the venous pressure of 80% corresponded approximately to a 50% diminution in the outflow.

Ergotamine injected at a dose of 5 to 10 μg./kg. in the dog anaesthetized with chloralose exerted a distinct cerebral vasoconstrictor action, which was clearly demonstrated by the fall in the peripheral jugular pressure and the decrease of the blood flow in the cerebral vein.

The main reason for the conflicting results obtained by various authors on the cerebral vascular action of ergotamine may be due to the high susceptibility of the cerebral vessels to various noxious and toxic agents. It has previously been shown that, under some experimental conditions such as barbiturate anaesthesia, hypercapnia, and minor traumatic shock, adrenaline and noradrenaline do not have a vasoconstrictor action (Bovet *et al.*, 1957). The appearance of this refractoriness to the vasoconstrictor action of the drugs is usually coupled with a progressive and marked fall in the peripheral jugular pressure. Similar factors manifested themselves in the response to ergotamine. It is clear that the cerebral vasoconstrictor effect of ergotamine was markedly affected by the initial level of the peripheral jugular pressure. It may be totally absent in cases of refractoriness of the cerebral vessels in which the venous outflow was initially low. Thus some of the negative results reported in the literature may be attributed to the trauma induced by the technique employed.

The significance of the initial level of the peripheral jugular pressure at which cerebral vasoconstrictor action of ergotamine appeared is emphasized by the fact that this action of the alkaloid becomes much more evident after drugs such as 48/80 and strychnine which caused a marked rise in the cephalic venous pressure. This action of 48/80 on the venous pressure has previously been described (Virno *et al.*, 1956) and appears to be related to the histamine-liberator effect.

The action of strychnine on the cerebral circulation was due to an increase in the systemic arterial pressure and an active vasodilatation of the cerebral vessels. The fact that ergotamine provoked a strong cerebral vasoconstrictor action in animals which had received strychnine is particularly significant, as the effect of strychnine on the cerebral circulation is probably related to the analeptic action of strychnine. Thus the responses of the cerebral vessels in the anaesthetized dog receiving strychnine resemble more closely those in the normal rather than those in the anaesthetized animal.

The experiments on the effect of CO_2 and acidosis upon cerebral venous pressure demonstrate the rôle played by this factor in brain circulation (Bouckaert and Jourdan, 1949 ; Lennox and Gibbs, 1932 ; Schmidt, 1928). In the markedly hypercapnic animal, the vasoconstrictor effect of ergotamine appeared generally to be weak and transient, a fact which corroborates the previous observations on the lack of a cerebral vasoconstrictor action of adrenaline under respiratory acidosis (Bovet *et al.*, 1957).

The influence of ergotamine on the cerebral vascular action of other drugs may be considered next. The abolition of the action of adrenaline on the peripheral jugular pressure by such small doses of ergotamine as 5 to 10 μg./kg. cannot be ascribed to the anti-adrenaline action of the alkaloid, which only appears after administration of much larger quantities. Clearly, the suppression of the cerebral vascular action of adrenaline is related to the well-known vasoconstrictor action of the alkaloid. After ergotamine, the peripheral jugular pressure passively follows the changes in arterial pressure provoked by adrenaline, similar results having been obtained under various experimental conditions by Forbes, Finley, and Nason (1933), Schneider and Schneider (1934a) and Taeschler, Cerletti, and Rothlin (1952).

The influence of small doses of ergotamine on the cerebral vascular action of the various vasodilator agents here studied, namely 40/80, histamine, and CO_2, must be considered as a functional antagonism depending on the vasoconstrictor effect of the alkaloid. Experiments, undertaken

to compare the relative activity of ergotamine and adrenaline on cerebral nasal and renal vessels, showed that, whereas small doses of adrenaline generally provoked comparable effects on these three vascular sites, the action of similar doses of ergotamine was slight on the renal plethysmogram, moderate and often transient on the nasal vessels, and more pronounced and of longer duration on the cerebral vessels. This series of experiments clearly demonstrated a relative specificity of action of ergotamine on the cerebral vessels. The dose used experimentally (5 to 10 μg./kg.) corresponds to that commonly injected clinically (0.5 mg. or 7 μg./kg.) and these experiments on the dog confirm the observations in man (Lennox and von Storch, 1936; Von Storch, 1937; Graham and Wolff, 1938; Wolff, 1948) and support the cerebral vasoconstrictor explanation of the value of ergotamine in the relief of migraine.

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