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Effects of drugs on the cerebral circulation of the dog in relation to the cerebral oxygen consumption

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1 Drug effects were studied on the cerebral circulation by measuring the sagittal sinus outflow in the anaesthetized dog following the method of Michenfelder and by monitoring cerebral oxygen consumption. Systemic aortic pressure, heart rate and spinal fluid pressure were also studied.

2 Since dilatation of cerebral vessels was observed in nearly all the preparations after inhalation of CO_2, it was thought that gross extracerebral contamination was virtually eliminated in this preparation. A close correlation was observed between the oxygen consumption of the brain as a whole and the sagittal sinus outflow ($r = 0.93$, $P < 0.001$); therefore it became feasible to differentiate the direct effects of drugs on cerebral blood vessels from indirect ones attributable to changes in the cerebral oxidative metabolism.

3 Sodium pentobarbitone (5 mg kg^{-1}, i.v.), reduced the cerebral venous outflow and caused a decrease in the oxygen consumption. Pentylenetetrazol (30 mg kg^{-1} i.v.) and bemegride (5 mg kg^{-1} i.v.) produced an increase in the blood flow and a corresponding increase in the cerebral oxygen consumption. Thus, it was concluded these substances had no direct effects on the cerebral blood vessels.

4 Acetazolamide (10 mg kg^{-1}, i.v.), a carbonic anhydrase inhibitor, produced a marked and sustained vasodilatation after a latent period of 0.5–1 min. There was no increase in the cerebral oxygen consumption. A similar pattern was seen after CO_2 had been inhaled. Methylergometrine and dihydroergotamine (20 μg kg^{-1} i.v.) induced a prolonged vasoconstriction of the cerebral vascular bed without any changes in the oxygen consumption of the brain. Therefore this method can discriminate between indirect or direct effects of drugs on cerebral vascular outflow.

Introduction

Cerebral blood flow changes little over a wide range of arterial blood pressure, yet it responds quickly and appropriately to a change in brain metabolism (Kuschinsky & Wahl, 1978). Thus, in analysing the effects of drugs on cerebral blood flow, it is important to differentiate direct effects on the cerebral vessels from indirect effects due to changes in cerebral metabolism. The purpose of the present study was to establish a routine method for studying the effects of drugs on the cerebral circulation of the dog, the animal most commonly used in cardiovascular research. The technique of direct measurement of the canine cerebral blood flow as devised by Michenfelder, Messick & Theye (1968) was adopted. Several reference drugs with known effects on the human cerebral circulation, were studied on cerebral flow in relation to cerebral oxygen consumption, using the principle normally applied to the study of the drugs on the coronary circulation.

Methods

Dogs of either sex weighing 7 to 16 kg were anaesthetized with an intravenous injection of α-chloralose (45 mg kg^{-1}) and urethane (450 mg kg^{-1}) after premedication with morphine hydrochloride (1.5 mg kg^{-1} s.c.).

The technique used to measure the cerebral venous outflow is a modification of that described by Michenfelder *et al.* (1968) and is illustrated in Figure 1. Occlusion of the ethmoidal veins was not carried out for it required extensive removal of bone and was fraught with persistent haemorrhage. Furthermore, Michenfelder *et al.* have shown that flow measured before and after occlusion was not significantly different.

The sagittal sinus was exposed by a midline frontal-occipital incision and a craniotomy was performed using a dental drill (Beaver-Labo, Osada Electric Co.). To rule out contamination from the extracranial circulation, bilateral incisions of the frontal-

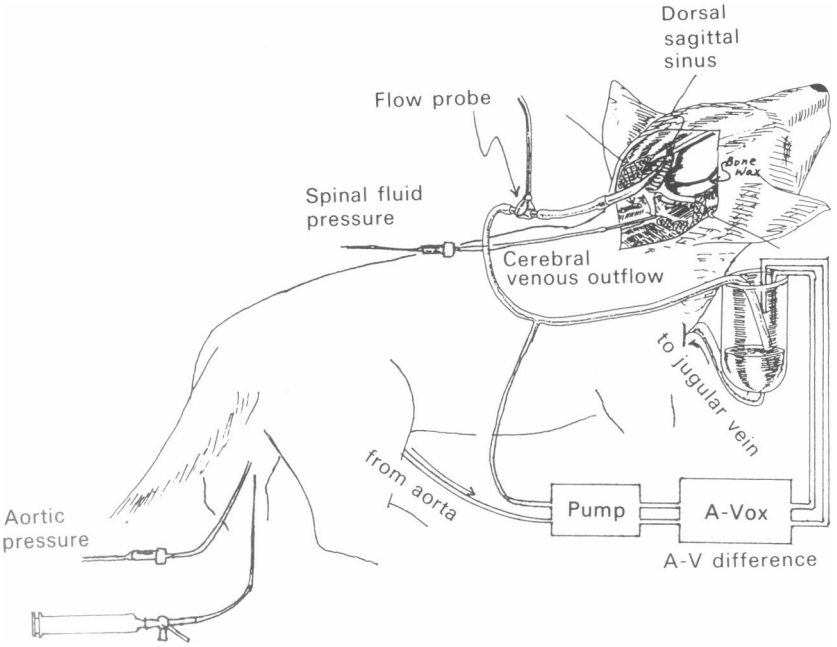


Figure 1 Schematic drawing of the preparation used to study the cerebral circulation after the method of Michenfelder *et al.* (1968).

occipital bone were made by a dental drill exposing the brain as in Figure 1 and the bone edges were packed with bone wax to occlude the diploic veins (Lukens Bone Wax Code 900, Tokyo M.I. Co.). The sagittal sinus was cannulated with a tapered polyethylene cannula after the peripheral sagittal sinus had been packed at sites just anterior to the junction of the lateral sinus and straight sinus with small pieces of gelatin sponge (Spongel, Yamanouchi). The blood outflow from the sinus was measured by an electromagnetic flowmeter (Statham SP 2201, Statham Instrument) and collected into a venous reservoir, which drained into the jugular vein.

To measure the arterio-venous difference of the blood oxygen content, arterial blood was withdrawn from the aorta through a catheter inserted via a femoral artery, while a portion of the sagittal sinus blood was withdrawn distal to the flow probe. They were diverted to an arterio-venous oxygen difference recorder (A-Vox System Co.), being pumped at a constant rate of 7 ml min^{-1} by a roller pump (LKB 2115). The oxygen consumption of the brain was calculated by multiplying the A-V oxygen difference (vol. %) by the corresponding cerebral venous outflow (ml min^{-1} 100 g^{-1} brain), according to Fick's principle. The blood leaving the A-Vox was returned to the jugular vein through a venous reservoir together with the sagittal sinus blood.

Before cannulation of the sagittal sinus, dogs were heparinized intravenously with 500 u kg^{-1} of heparin and a further 100 u kg^{-1} was added every hour thereafter.

By means of a catheter inserted in the other femoral artery, aortic pressure was monitored with a pressure transducer (Statham P50, Statham Instrument) and a carrier amplifier (Sanei Instrument 1236). The pulse rate was measured continuously with a cardiac tachometer (Sanei Instrument 2130) triggered by the aortic pressure pulses. The spinal fluid pressure was registered from the cisterna magna. All these parameters were displayed on an ink-writing recorder (Linearcorder, Watanabe Instrument WTR 3001).

The dogs were ventilated with room air by a respirator (Takashima Shoten TB-100 II) and pH, $P_{O_2}$and P_{CO_2} values were measured intermittently using a blood gas analyser (Radiometer BGA 3A-MK2, Radiometer Co.). The pH of the arterial blood was maintained around 7.4 by adjusting the ventilation rate and tidal volume. Arterial blood pH, P_{O_2} and P_{CO_2} were 7.40 ± 0.01 ($n = 24$), 116.2 ± 2.9 mmHg ($n = 24$) and 35.8 ± 1.3 mmHg ($n = 24$), respectively at the time of starting the experiment.

At the outset the possibility of the existence of anastomoses between the intracranial and extracranial circulation was checked with inhalation of CO_2. Preparations were discarded unless they showed an

unequivocal increase in sagittal sinus outflow and in spinal fluid pressure.

After the experiments the fore-brain (without the cerebellum) was removed and weighed so that cerebral venous outflow and oxygen consumption could be expressed per min and per 100 g of brain. On the basis of the autopsy data of Michenfelder *et al.* (1968) the weight of the brain drained by the sagittal sinus was taken to be 43% of the total brain weight.

Drugs were administered over 10 s through a fine polyethylene tubing inserted into the femoral vein and flushed with 1 ml of saline. In order to examine the effects of carbon dioxide (CO_2) gas inhalation on the cerebral circulation and systemic haemodynamics, CO_2 was blown directly into an inspiratory channel of the respirator through a gas volume regulator (Sharp). The carbon dioxide tension, oxygen tension and pH in the arterial and venous blood were checked before and during the inhalation of CO_2 gas.

Drugs used were heparin sodium (Wako Pure Chemical Industries), adenosine (Sigma), nitroglycerine (Nihonkayaku), pentobarbitone sodium (Abbott Laboratories), bemegride (Yamanouchi), pentylenetetrazol (Sigma), dihydroergotamine (Sandoz) and methylergometrine maleate (Mochida).

Results

The relation between cerebral venous outflow and cerebral oxygen consumption

The cerebral blood flow determined by Michenfelder's method was 16.6 ± 1.1 ml min^{-1} 100 g^{-1} brain ($n = 19$) and the cerebral oxygen consumption, 1.01 ± 0.05 ml min^{-1} 100 g^{-1} brain ($n = 19$). The cerebral oxygen consumption determined at steady states during spontaneous or artificial respiration was compared with the corresponding cerebral sinus outflow. There was an excellent linear correlation ($r = 0.93$, $P < 0.001$) between these two parameters as shown in Figure 2. Thus, we felt justified in applying the same principle to analyse the effects of drugs on the cerebral circulation in relation to changes in the cerebral oxygen consumption as was used previously on the coronary circulation (Imai, Otorii, Takeda & Katano, 1975).

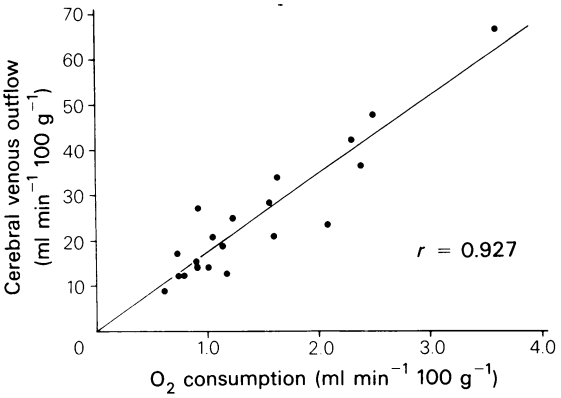


Figure 2 The relationship between cerebral venous outflow and oxygen consumption.

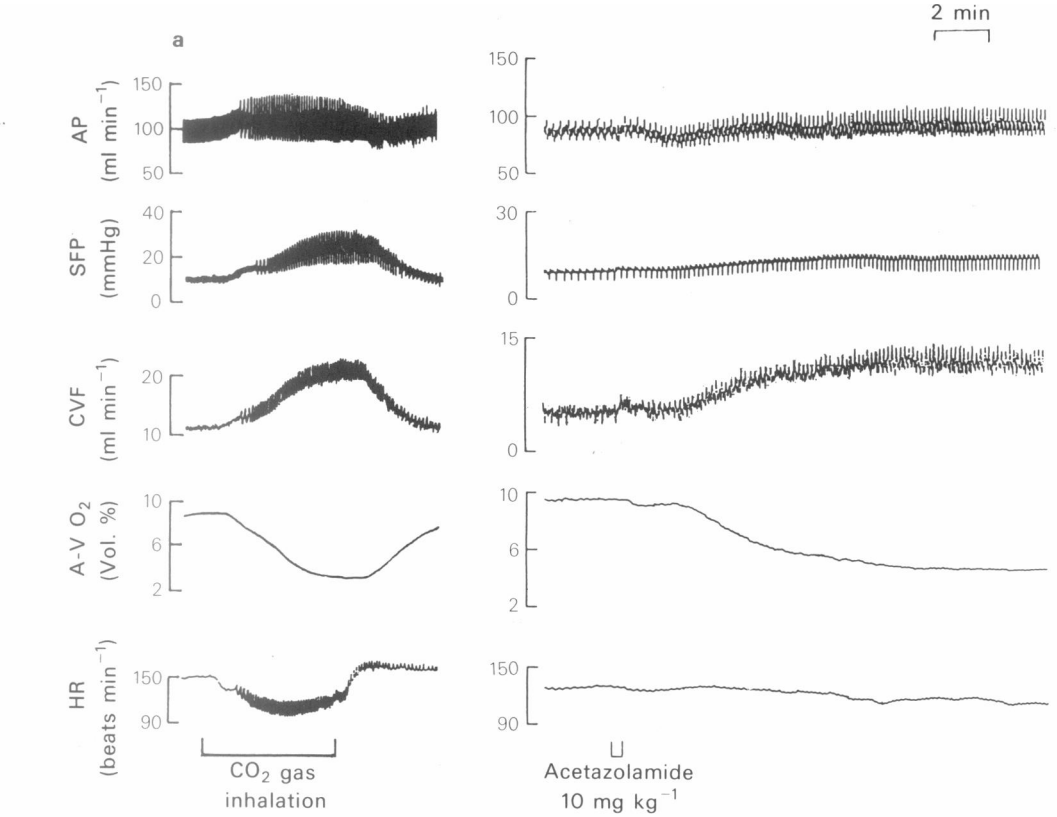
Effects of various agents on the cerebral circulation and systemic haemodynamics

(a) *Carbon dioxide inhalation and acetazolamide* Among the various agents and procedures used in the present study, CO_2 gas inhalation and intravenous acetazolamide (10 mg kg^{-1} to 30 mg kg^{-1}) induced the most pronounced changes in cerebral venous outflow. Inhalation of CO_2 caused a significant increase in the cerebral venous outflow accompanied

Table 1 Effects of CO_2 gas inhalation and acetazolamide (30 mg kg^{-1}, i.v.) on cerebral venous outflow and pH and CO_2 tensions in arterial and venous blood

	CO_2 gas inhalation			*Acetazolamide*		
	n	*before*	*after*	n	before	after
CVF (ml min^{-1} 100 g^{-1})	(6)	11.8 ±2.0	25.4 ± 7.4*	(5)	12.6 ±2.2	16.5 ±1.7*
pH A	(5)	7.37±0.02	7.15±0.04**	(4)	7.35±0.02	7.32±0.01*
pH V	(5)	7.32±0.02	7.17±0.01**	(4)	7.30±0.01	7.30±0.01
Pa_{CO_2} (mm Hg)	(5)	35.8 ±2.5	84.7 ±13.2**	(5)	31.4 ±4.5	38.7 ±3.1**
PV_{CO_2} (mm Hg)	(5)	50.5 ±3.4	79.8 ±7.7**	(5)	50.4 ±5.1	47.6 ±3.7

*: $P < 0.05$; **: $P < 0.01$.



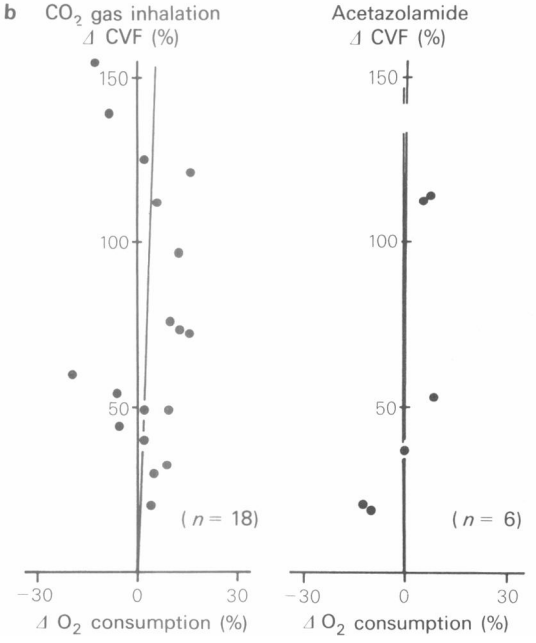
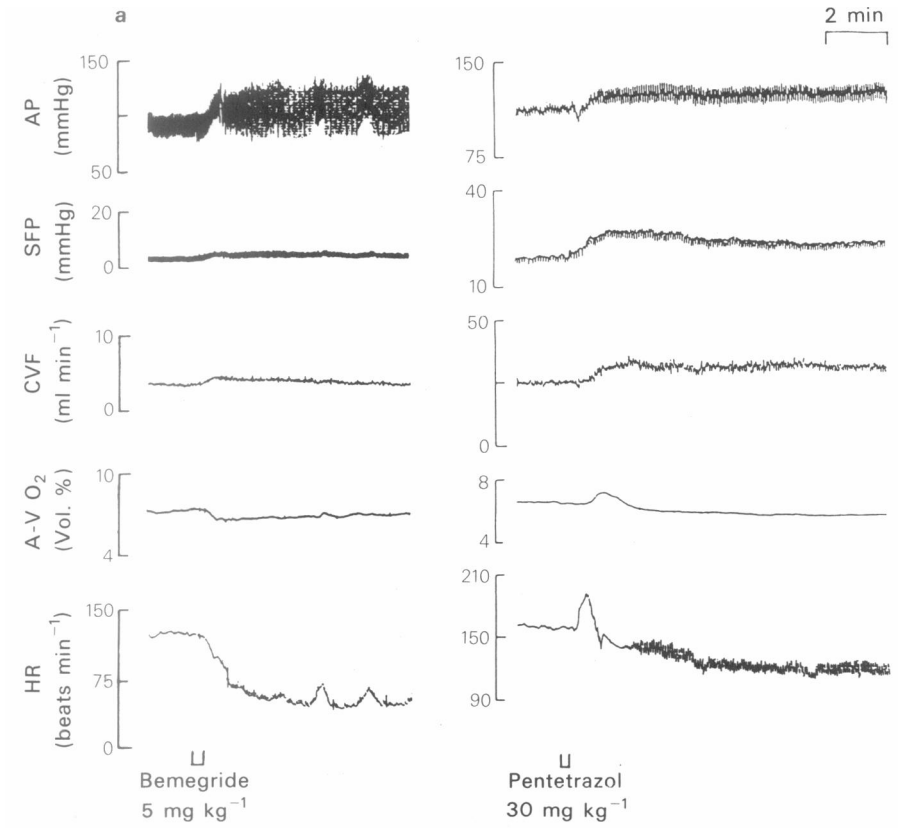
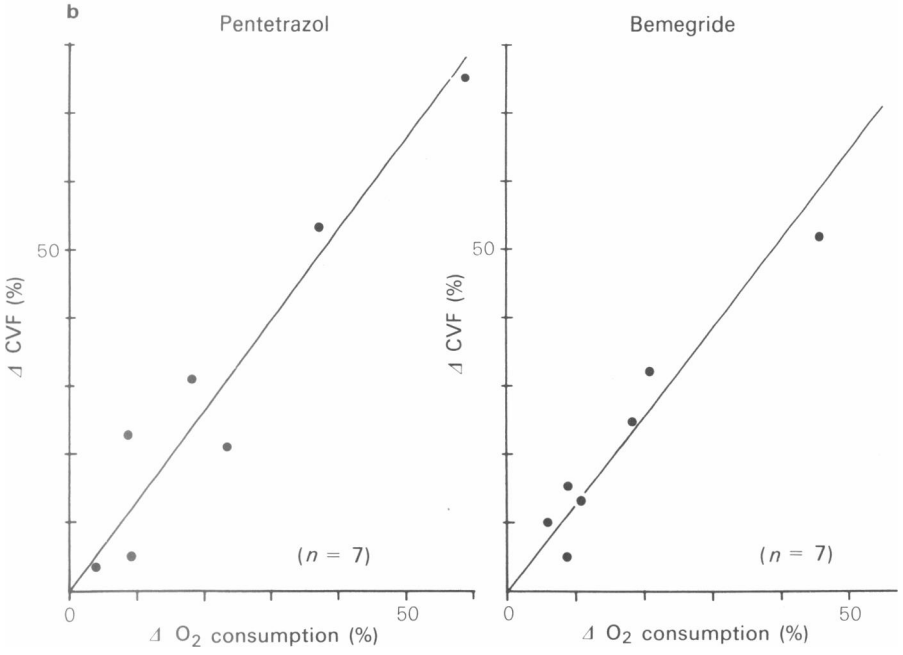


Figure 3 Effects of CO_2 gas inhalation and intravenous acetazolamide on the cerebral circulation and systemic haemodynamics. (a) Typical experimental records: AP = aortic pressure; SFP = spinal fluid pressure; CVF = cerebral venous outflow; A-V O_2 = arterio-venous difference of the oxygen content in the cerebral blood; and HR = heart rate. (b) The relationship between changes in cerebral venous outflow produced by CO_2 gas inhalation and acetazolamide and changes in cerebral oxygen consumption. ΔCVF: changes in the cerebral venous outflow expressed as percentage increase over the initial values. ΔO_2 consumption: changes in the cerebral O_2 consumption expressed as percentage increase or decrease from the initial values. Numbers in parentheses represent the number of experiments.

Figure 4 Effects of bemegride and pentetrazole on the cerebral venous outflow and systemic haemodynamics. (a) Typical experimental records: Abbreviations are the same as in Figure 3(a). (b) The relationship between changes in cerebral venous outflow produced by bemegride and pentylenetetrazol and changes in cerebral oxygen consumption. Abbreviations are the same as in Figure 3(b).


a
2 min
AP (mmHg)
150
50
150
75
SFP (mmHg)
20
0
40
10
CVF (ml min⁻¹)
10
0
50
0
A-V O2 (Vol. %)
10
4
8
4
HR (beats min⁻¹)
150
75
0
210
150
90
Bemegride
5 mg kg⁻¹
Pentetrazol
30 mg kg⁻¹


b
Pentetrazol
Bemegride
Δ CVF (%)
50
0
50
(n = 7)
Δ O2 consumption (%)

by a decrease in the A-V oxygen difference and an increase in the spinal fluid pressure. The aortic pressure rose slightly and the heart rate was reduced during the CO_2 inhalation. Periodical changes observed in these parameters were due to an enhanced spontaneous breathing caused by CO_2 gas inhalation. Acetazolamide produced a prolonged increase in the sagittal sinus outflow associated with a decrease in A-V oxygen difference and a gradual, but small increase in spinal fluid pressure after a latent period of 0.5–1 min. The aortic pressure and the heart rate did not change. Figure 3a shows typical experimental records.

Figure 3b depicts the relationship between the changes in cerebral venous outflow and oxygen consumption produced by CO_2 gas inhalation and acetazolamide; in each case a marked increase in the cerebral venous outflow occurred without any appreciable change in the oxygen consumption of the brain.

Changes observed in the blood gas tensions and pH are summarized in Table 1. Carbon dioxide gas inhalation provoked significant changes in CO_2 gas tension of the arterial and venous blood, while acetazolamide produced significant changes in CO_2 gas tension and pH only in arterial blood at the time of establishment of the maximal effect.

(b) *Bemegride and pentylenetetrazol* Bemegride (2–5 mg kg^{-1} i.v.) and pentylenetetrazol (30–60 mg kg^{-1} i.v.) each induced a dose-related prolonged increase in the cerebral venous outflow with a decrease in the A-V oxygen difference. Correspondingly, the spinal fluid pressure rose and the heart rate was decreased (Figure 4a). Both drugs stimulated respiration and tremors or twitches of skeletal muscles were observed in almost all the dogs, as reflected in the irregular experimental records.

The relationship between changes in the cerebral venous outflow and cerebral oxygen consumption produced by bemegride and pentylenetetrazol is shown in Figure 4b, in which a close correlation may be seen.

(c) *Sodium pentobarbitone* Sodium pentobarbitone (1–10 mg kg^{-1} i.v.) caused a slight fall in aortic pressure and a sustained decrease in both heart rate and spinal fluid pressure. A protracted fall in cerebral venous outflow was observed in association with an elevation of the A-V oxygen difference. These changes are depicted graphically and as original experimental records in Figure 5a and b.

(d) *Adenosine and nitroglycerine* Adenosine (0.3–3 mg kg^{-1} i.v.) and nitroglycerine (30–100 μg kg^{-1} i.v.) each produced a transient but steep decrease in the aortic pressure. There was a

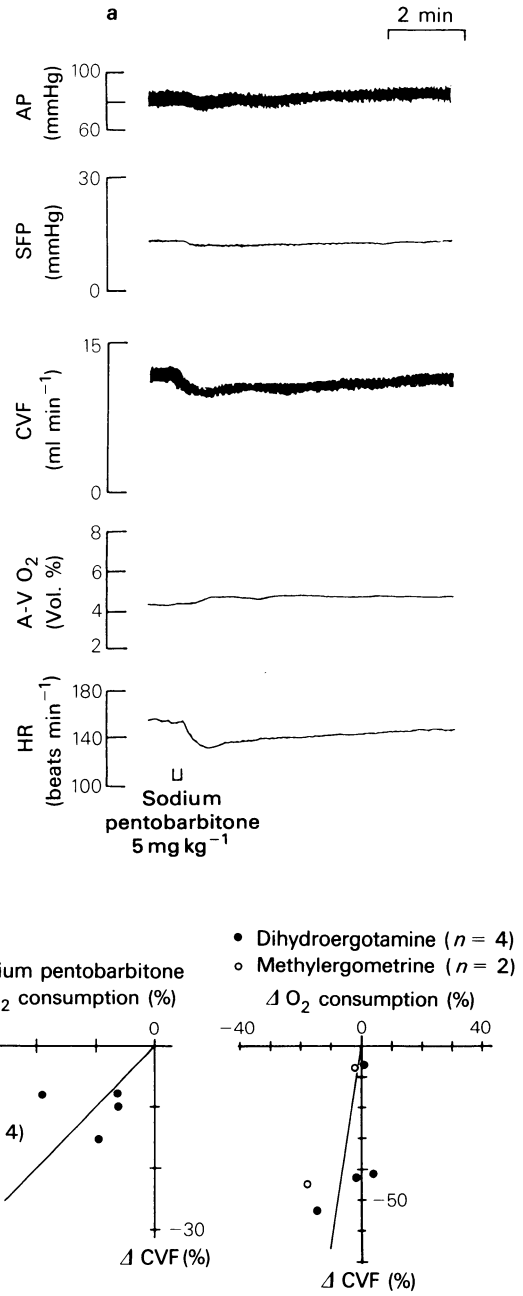
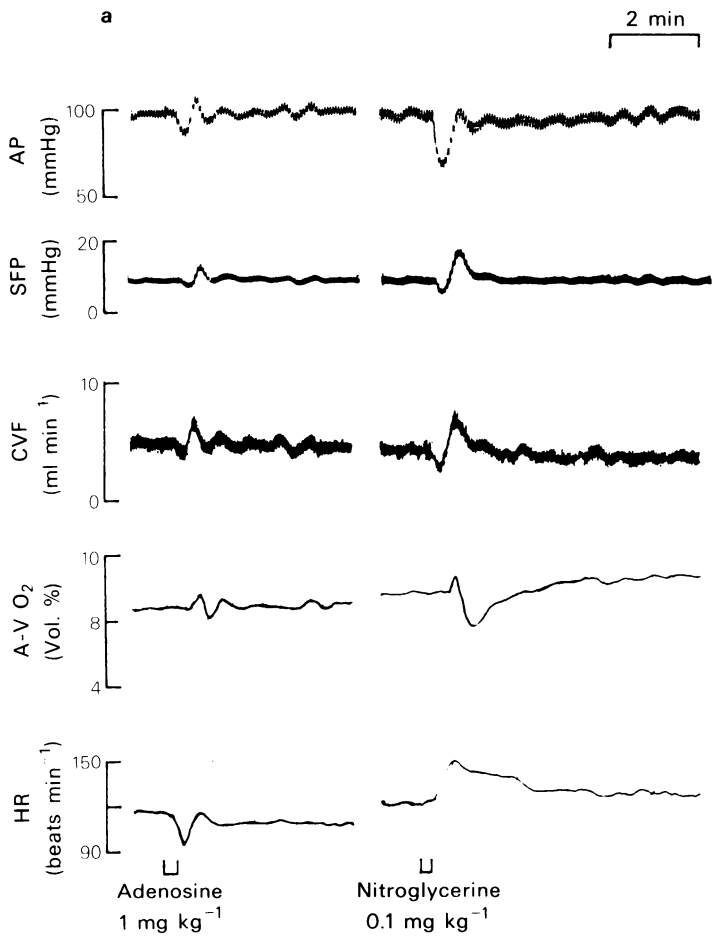


Figure 5 Effects of sodium pentobarbitone on the cerebral circulation and systemic haemodynamics (a) Typical experimental record: Abbreviations are the same as in Figure 3(a). (b) The relationship between changes in cerebral venous outflow produced by sodium pentobarbitone and ergot alkaloids and changes in cerebral oxygen consumption. Abbreviations are the same as in Figure 3(b).



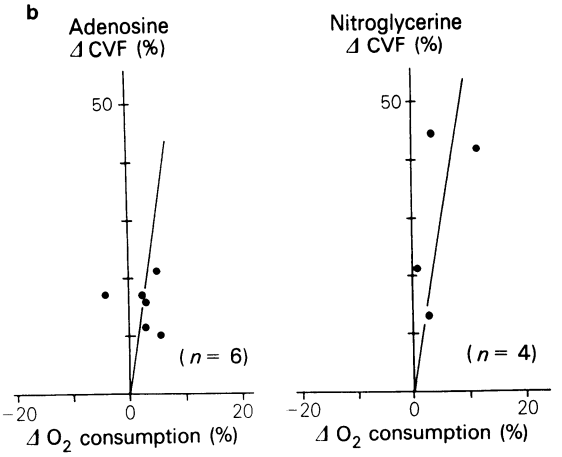


Figure 6 Effects of adenosine and nitroglycerine on the cerebral circulation and systemic haemodynamics. (a) Typical experimental records: Abbreviations are the same as in Figure 3(a). (b) The relationship between changes in cerebral venous outflow produced by adeosine and nitroglycerine and changes in cerebral oxygen consumption. Abbreviations are the same in Figure 3(b).

transient decrease in the heart rate after adenosine, while nitroglycerine produced an increase (see Figure 6a). The sagittal sinus outflow increased significantly after a slight decrease, corresponding to an abrupt fall in aortic pressure immediately after administration of each drug. The spinal fluid pressure changed as did the cerebral venous outflow, while the A-V oxygen difference altered in the opposite direction as shown in Figure 6a.

When changes in cerebral venous outflow caused by adenosine and nitroglycerine were plotted against cerebral oxygen consumption, each drug could be seen to augment cerebral venous outflow without changing the oxygen consumption of the brain (Figure 6b).

(e) *Ergot alkaloids* Methylergometrine ($20-100\,\mu g\,kg^{-1}$ i.v.) and dihydroergotamine ($20\,\mu g\,kg^{-1}$ i.v.) each produced a prolonged decrease in the cerebral sinus outflow, which was associated with a fall of the spinal fluid pressure. The arteriovenous oxygen difference was elevated and remained higher whilst the cerebral venous outflow was depressed. The aortic pressure rose slightly and the heart rate was decreased slightly. Both ergot alkaloids decreased the cerebral venous outflow without any marked change in the oxygen consumption of the brain (for convenience the graph is shown in Figure 5b.)

Discussion

In his monograph on the cerebral circulation, Purves (1972) wrote: '... the cat and the dog are not satisfactory experimental animals for the measurement of cerebral blood flow when the method involves an estimation of carotid arterial or venous blood flow. A more satisfactory animal is the monkey in which there appears to be a much more complete separation of the intra- and extracranial circulations'. However, the monkey is not a suitable animal for routine experimental work. Furthermore, Purves was more concerned with physiological aspects of the circulation such as the absolute value of cerebral blood flow, while we were much more concerned with pharmacological aspects. We have, therefore, re-examined the possibility of using the dog.

As a measure of cerebral blood flow, the cerebral venous outflow was determined following the method devised by Michenfelder *et al.* (1968). It offers advantages over other direct-flow methods in that it causes minimal surgical disruption of the normal cerebrovascular anatomy and virtually eliminates extracerebral contamination. In addition, the venous blood used for the measurement of metabolic components is exclusively representative of that area of the brain from which the flow is measured, primarily the cerebral hemispheres. In most of our preparations, inhalation of CO_2 produced a definite increase and administration of barbiturates, a definite decrease in the cerebral sinus outflow, indicating that it represented primarily venous blood from intracranial vessels. It is well known that CO_2 is a specific dilator of cerebral vessels; and a reduction of cerebral blood flow by barbiturates in man and experimental animals has been substantiated by many authors (Schmidt, Kety & Pennes, 1945; Homburger, Himwich, Esten, York, Maresca & Himwich, 1946; Himwich, Homburger, Maresca & Himwich, 1947; McCall & Taylor, 1952; Daweke, Hahn & Oberdorf, 1959; Gottstein, Bernsmeier, Lehn & Niedermayer, 1961; Pierce, Lambertsen, Deutsch, Chase, Linde, Dripps & Price, 1962; Rosomoff, 1965). Purves' (1972) criticism of the venous outflow method was principally aimed at the technique of Rapela & Green (1964). Preliminary experiments conducted by us with their method showed that the responses to CO_2 or barbiturates were much more capricious than those of Michenfelder's preparation.

As early as 1945, Schmidt *et al.* studied in monkeys the relationships between A-V oxygen difference, blood flow and O_2 uptake of the brain and found that the correlation between the blood flow and O_2 uptake was by far the best. Similar correlation was later found by Kety (1950) in man. In the present experiments a significant linear correlation was found between cerebral sinus outflow (Y) and cerebral oxygen uptake (X), corresponding to an equation: $Y = aX$ (a = constant). On the basis of this finding, we reasoned that it was possible to discriminate between the effects of substances on cerebral blood vessels and those on oxygen consumption of the brain, as we had done earlier with the coronary circulation (Imai *et al.*, 1975).

Theoretically, a substance lacking a direct effect on cerebral vessels but stimulating cerebral oxidative metabolism would increase the cerebral oxygen consumption from X_1 to X_2, thereby increasing blood flow from Y_1 to Y_2. From the previous equation, the following relationship is seen:

$$\frac{Y_2}{Y_1} = \frac{X_2}{X_1}$$

which can be rearranged to become:

$$\frac{Y_2 - Y_1}{Y_1} = \frac{X_2 - X_1}{X_1}$$

This equation means that the percentage increase in cerebral oxygen consumption should be equal to the percentage increase in cerebral blood flow, if a substance increases flow merely by increasing the oxygen consumption.

As a corollary, a constriction of the cerebral blood vessels can be inferred if the percentage increase in cerebral oxygen consumption is greater than the percentage increase in cerebral blood flow. Alternatively, a disproportionately greater increase in the cerebral blood flow indicates a direct dilatory effect of a substance on the cerebral blood vessels.

Convulsant drugs such as pentylenetrazol produce an increase in cerebral blood flow secondarily to an increase in both oxygen consumption and cerebral activity (Schmidt *et al.*, 1945; Fujita, 1956; Ingvar, Lübbers & Siesjö, 1962; Plum, Posner & Troy, 1968). In the present study, pentylenetetrazol and bemegride each produced an increase in the cerebral blood flow associated with an increase in the cerebral oxygen consumption of the brain. As shown in Figure 4, the percentage increase in cerebral blood flow produced by these compounds was found to be equal to the percentage increase in the cerebral oxygen uptake, indicating that the increased flow was entirely due to the raised oxygen demand resulting from the increased brain activity. This is in harmony with the findings of Schmidt *et al.* (1945) that pentylenetetrazol failed to alter blood flow or metabolic rate when no convulsions occurred.

On the same principle it is made clear that the decreased cerebral blood flow produced by pentobarbitone was due not to a direct constriction of cerebral blood vessels, but to a decrease in the cerebral oxidative metabolism. There is general agreement that barbiturates depress cerebral oxygen consumption (Homburger *et al.*, 1946; Himwich *et al.*, 1947; McCall & Taylor, 1952; Fazekas & Bessman, 1953; Gottstein *et al.*, 1961; Pierce *et al.*, 1962). Some researchers have reported no change or even an increase in the cerebral blood flow with barbiturates, but these may have resulted from depression of the respiratory activity and the consequent increase in arterial P_{CO_2} which would oppose the vasoconstriction caused by reduced O_2 consumption.

We studied adenosine because it has been postulated as a metabolic regulator of the cerebral circulation (Berne, Rubio & Curnish, 1974; Winn, Rubio & Berne, 1981); and nitroglycerine as a representative vasodilator, one of whose principal adverse effects, headache, being generally attributed to its cerebral vasodilator action (Elkind, Friedman & Grossman, 1964). Both of these agents produced a definite increase in the cerebral sinus outflow, after a slight decrease, which was not accompanied by significant changes in the cerebral oxygen consumption. Therefore, it is clear that both drugs have a direct vasodilator effect on the cerebral vasculature. This is the first clear-cut demonstration of an increase in canine cerebral blood flow by adenosine. Buyniski & Rapela (1969) and Emerson & Raymond (1981) failed to show an increase in the cerebral blood flow in the dog and ascribed it to poor penetration of the blood-brain barrier by this substance. It is possible that the venous outflow in their preparations (Rapela & Green's preparation) was grossly contaminated with extracranial blood, and that a marked increase in the extracranial blood flow resulted in a decrease in the intracranial blood flow (the so-called 'steal' phenomenon). In the present study, at higher doses of both drugs the cerebral venous outflow did not increase. This may have been due to a marked fall in blood pressure which was observed after administration of these two agents.

As already stated in a previous section, it is well known that inhaled CO_2 dilates cerebral vessels (Raper, Kontos & Patterson, 1971; Shinohara, 1973). Acetazolamide, a carbonic anhydrase inhibitor, has been shown to enter selected areas of the brain in significant quantities (Roth, Schoolar & Barlow, 1959) and produce a marked cerebral vasodilatation (Ehrenreich, Bunns, Alman & Fazekas, 1961; Shinohara, 1973). In the present study both the inhalation of CO_2 gas and intravenous administration of acetazolamide produced a marked increase in the cerebral venous outflow without any change in the oxygen consumption of the brain, indicating a direct cerebral vasodilatory effect. Carbon dioxide gas inhalation increased the CO_2 tension and lowered the pH of arterial and venous blood, while acetazolamide increased the CO_2 tension and reduced pH only in arterial blood as reported by Atkinson & Ward (1964). Thus, in each case, it may be that the vasodilatation is associated with an increase in arterial P_{CO_2} and/or a decrease in arterial pH.

Methylergometrine and dihydroergotamine decreased the cerebral blood flow without producing any change in the oxygen consumption of the brain, confirming previous reports of a significant cerebral vasoconstriction (Dumke & Schmidt, 1943; Carpi & Virno, 1957) produced by ergot alkaloids.

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References

ATKINSON, J.R. & WARD, JR. A.A. (1964). Effect of acetazolamide on brain and blood pH. *Neurology*, **14**, 561–564.

BERNE, R.M., RUBIO, R. & CURNISH, R.R. (1974). Release of adenosine from ischemic brain. Effect on cerebral vascular resistance and incorporation into cerebral adenosine nucleotides. *Circulation Res.*, **35**, 262–271.

BUYNISKI, J.P. & RAPELA, C.E. (1969). Cerebral and renal

vascular smooth muscle responses to adenosine. *Am. J. Physiol.*, **217,** 1660–1664.

CARPI, A. & VIRNO, M. (1957). The action of ergotamine on the intracranial venous pressure and on the cerebral venous outflow of the dog. *Br. J. Pharmac. Chemother.*, **12,** 232–239.

DAWEKE, H., HAHN, F. & OBERDORF, A. (1959). Einfluss von barbituratantagonistischen Analepticis auf EEG, Sauerstoffaufnahme und Durchbutung des Gehirns bei schwerer Veronalvergiftung des Hundes. *Nauny-Schmiedebergs Arch. exp. Path. Pharmak.*, **235,** 247–260.

DUMKE, P.R. & SCHMIDT, C.F. (1943). Quantitative measurements of cerebral blood flow in the macacque monkey. *Am. J. Physiol.*, **138,** 421–431.

EHRENREICH, D.L., BURNS, R.A., ALMAN, R.W. & FAZEKAS, J.F. (1961). Influence of acetazolamide on cerebral blood flow. *Arch. Neurol.*, **5,** 227–232.

ELKIND, A.H., FRIEDMAN, A.P. & GROSSMAN. J. (1964). Cutaneous blood flow in vascular headaches of the migraine type. *Neurology*, **14,** 24–30.

EMERSON, JR. T.E. & RAYMOND, R.M. (1981). Involvement of adenosine in cerebral hypoxic hyperemia in the dog. *Am. J. Physiol.*, **241,** H134–H138.

FAZEKAS, J.F. & BESSMAN, A.N. (1953). Coma mechanisms. *Am. J. Med.*, **15,** 804–812.

FUJITA, N. (1956). Pharmacological study on electrical activity and oxygen consumption of brain cortex. *Jap. J. Pharmac.*, **5,** 151–173.

GOTTSTEIN, U., BERNSMEIER, A., LEHN, H. & NIEDERMAYER, W. (1961). Hämodynamik und Stoffwechsel des Gehirns bei Schlafmittelvergiftung. *Dt. med. Wschr.*, **86,** 2170–2176.

HIMWICH, W.A., HOMBURGER, E., MARESCA, R. & HIMWICH, H.E. (1947). Brain metabolism in man: Unanesthetized and in pentothal narcosis. *Am. J. Psychiat.*, **103,** 689–696.

HOMBURGER, E., HIMWICH, W.A., ESTEN, B., YORK, G., MARESCA, R. & HIMWICH, H.E. (1946). Effect of pentothal anesthesia on canine cerebral cortex. *Am. J. Physiol.*, **147,** 343–345.

IMAI, S., OTORII, T., TAKEDA, K. & KATANO, Y. (1975). Coronary vasodilatation and adrenergic receptors in the heart and coronary vasculature. *Jap. J. Pharmac.*, **25,** 423–432.

INGVAR, D.H., LÜBBERS, D.W. & SIESJÖ, B.K. (1962). Normal and eileptic EEG patterns to cortical oxygen tension in the cat. *Acta. physiol. scand.*, **55,** 210–224.

KETY, S.S. (1950). Circulation and metabolism of the human brain in health and disease. *Am. J. Med.*, **8,** 205–217.

KUSCHINSKY, W. & WAHL, M. (1978). Local chemical and neurogenic regulation of cerebral vascular resistance. *Physiol. Rev.*, **58,** 656–689.

McCALL, M.L. & TAYLOR, H.W. (1952). Effects of barbiturate sedation on the brain in toxemia of pregnancy. *J. Am. med. Ass.*, **149,** 51–54.

MICHENFELDER, J.D., MESSICK, J.M. & THEYE, R.A. (1968). Simultaneous cerebral blood flow measured by direct and indirect methods. *J. Surg. Res.*, **8,** 475–481.

PIERCE, JR. E.C., LAMBERTSEN, C.J., DEUTSCH, S., CHASE, P.E., LINDE, H.W., DRIPPS, R.D. & PRICE, H.L. (1962). Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. *J. clin. Invest.*, **41,** 1664–1671.

PLUM, F., POSNER, J.B. & TROY, B. (1968). Cerebral metabolic and circulatory responses to induced convulsions in animals. *Arch. Neurol.*, **18,** 1–13.

PURVES, M.J. (1972). *The Physiology of the Cerebral Circulation.* Cambridge: Cambridge Univ. Press

RAPELA, C.E. & GREEN, H.D. (1964). Autoregulation of canine cerebral blood flow. *Circulation. Res.*, **15,** Suppl., I205–I211.

RAPER, A.J., KONTOS, H.A. & PATTERSON, JR. J.L. (1971). Response of pial precapillary vessels to changes in arterial carbon dioxide tension. *Circulation. Res.*, **28,** 518–523.

ROSOMOFF, H.L. (1965). Adjuncts to neurosurgical anesthesia. *Br. J. Anaesth.*, **37,** 246–261.

ROTH, L.J., SCHOOLAR, J.C. & BARLOW, C.F. (1959). Sulfur-35 labeled acetazolamide in cat brain. J. Pharmac. exp. Ther., **125,** 128–136.

SCHMIDT, C.F., KETY, S.S. & PENNES, H.H. (1945). The gaseous metabolism of the brain of the monkey. *Am. J. Physiol.*, **143,** 33–52.

SHINOHARA, Y. (1973). Mechanism of chemical control of cerebral vasomotor activity. *Neurology*, **23,** 186–195.

WINN, H.R., RUBIO, G.R. & BERNE, R.M. (1981). The role of adenosine in the regulation of cerebral blood flow. *J. Cerebral Blood Flow and Metabolism*, **1,** 239–244.

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