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CEREBRAL CIRCULATORY AND METABOLIC EFFECTS OF 5-HYDROXYTRYPTAMINE IN ANAESTHETIZED BABOONS

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SUMMARY

1. The cerebral circulatory effects of the intracarotid administration of 5-hydroxytryptamine were examined in anaesthetized baboons. Cerebral blood flow was measured by the intracarotid ^{133}Xe technique, cerebral O_2 consumption and glucose uptake were measured as indices of brain metabolism and electrocortical activity was continuously monitored.

2. Despite a marked reduction in the calibre of the internal carotid artery (assessed angiographically), the intracarotid infusion of 5-hydroxytryptamine 0·1 μg/kg.min did not effect any significant changes in cerebral blood flow, O_2 consumption or glucose uptake.

3. Following transient osmotic disruption of the blood-brain barrier with the intracarotid infusion of hypertonic urea, the same dose of 5-hydroxytryptamine effected a marked reduction in cerebral blood flow from 51 ± 2 to 36 ± 2 ml./100 g.min (mean $\pm$ S.E.; $P < 0{\cdot}01$). Both indices of cerebral metabolism were reduced significantly and the e.e.g. showed a more pronounced suppression-burst pattern.

4. We postulate that the cerebral circulatory responses to 5-hydroxytryptamine are dependent upon the integrity of the blood-brain barrier and the predominant effect of the intravascular administration of 5-hydroxytryptamine is on cortical activity or metabolism, rather than on cerebrovascular smooth muscle.

INTRODUCTION

Serotonin, or 5-hydroxytryptamine, is stored in high concentrations within both the circulating platelets (Garattini & Valzelli, 1965) and the neurones of the raphé complex which ascend from the brain stem to the

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cerebrum (Dahlström & Fuxe, 1964). However, the cerebrovascular actions and physiological role of 5-hydroxytryptamine are not clearly understood. The available studies on the cerebral circulatory effects of 5-hydroxytryptamine are somewhat conflicting, as discussed in a recent review (Edvinsson & MacKenzie, 1976).

The present investigation was undertaken in order to characterize the effects of 5-hydroxytryptamine on the cerebral circulation of anaesthetized baboons, and to examine two aspects of this relationship in particular. First, the observed changes in cerebral blood flow were correlated with brain metabolism (assessed by the cerebral metabolic rates for oxygen and glucose) and with cortical activity (assessed by electro-encephalography). Secondly, the relevance of the blood-brain barrier to the cerebral circulatory actions of systemic 5-hydroxytryptamine was examined by transiently disrupting the blood-brain barrier.

METHODS

General. Seven young, healthy baboons (*Papio anubis* and *P. cynocephalus*), of either sex and weighing between 10 and 30 kg, were sedated with 12–20 mg phencyclidine (I.M.). Anaesthesia was induced by the I.V. injection of sodium thiopentone (7·5 mg/kg) before the animals were intubated and connected to a positive pressure ventilator which delivered 75% nitrous oxide and 25% oxygen in open circuit. When surgery was completed, anaesthesia was maintained by half-hourly injections of phenycyclidine (2–5 mg, I.M.) in addition to the nitrous oxide. Suxamethonium (50 mg, I.M.) was administered very 30 min in order to assist in the control of ventilation with the respiratory pump. Depth of anaesthesia was gauged by the e.e.g. pattern, by the absence of pupillary reflexes and by the lack of pressor response following noxious stimuli.

A cannula was inserted into the abdominal aorta, via one femoral artery, in order to record mean arterial pressure; and a catheter was inserted into the inferior vena cava in order to administer a slow infusion of physiological saline and other drugs. The stroke volume of the ventilator was adjusted as necessary in order to maintain normocapnia ($P_{a,CO_2} \cong 40$ mmHg). End-tidal P_{CO_2} was monitored continuously and arterial blood samples were taken during every determination of cerebral blood flow in order to measure P_{CO_2}, P_{O_2} and pH. Body temperature was maintained around 37 °C with infra-red heating lamps.

Measurement of cerebral blood flow. A catheter was inserted centripetally into one linguo-facial artery. The main trunk of the external carotid artery and the superior thyroid artery were ligated on the same side, as was the ascending pharyngeal artery if this could be done without undue manipulation of the internal carotid artery. The ipsilateral scalp and temporalis were resected down to the level of the zygomatic arch, leaving the frontal, parietal and temporal areas of the calvarium denuded.

Cerebral blood flow was measured by the intracarotid ^{133}Xe technique. Approximately 250 μc ^{133}Xe (dissolved in 0·5 ml. sterile, heparinized saline) was injected into the internal carotid artery via the linguo-facial catheter. The gamma-ray emissions of the ^{133}Xe were detected by a collimated scintillation crystal attached to a photomultiplier, mounted over the ipsilateral temporo-parietal region. A 2·5 cm, thallium-activated sodium iodide crystal was used. The pulses from the photomultiplier were amplified and then subjected to pulse-height analysis (peak 81 keV ±

10%) before being fed into a ratemeter and a scaler. The ouptut from the ratemeter was displayed on a chart recorder. Cerebral blood flow was calculated from the height/area equation (Høedt-Rasmussen, Sveinsdottir & Lassen, 1966) as follows:

$$F = \frac{\lambda(H_i - H_{10}).60.100}{A_{10}},$$

where F = cerebral blood flow in ml. blood per 100 g brain tissue per min; λ = brain tissue/blood partition coefficient for ^{133}Xe, 1·1 ml./g being used in this study (Veall & Mallett, 1965); H_i = maximum initial height of the ^{133}Xe clearance curve in counts/sec; H_{10} = height of the clearance curve 10 min following the peak height, in counts/sec; and A_{10} = the total area under the clearance curve between H_i and H_{10} in counts. Appropriate calculations were made to subtract any background activity. The mean coefficient of variation for repeated measurements of cerebral blood flow is 7% at normocapnia, normoxia and normotension.

Measurement of cerebral oxygen and glucose consumption. The cerebral metabolic rate for oxygen utilization (CMR_{O_2}) was calculated from the product of cerebral blood flow and the corresponding arteriovenous oxygen content difference. Cerebral venous blood was obtained from the superior sagittal sinus. A burr hole was made over the sagittal suture approximately 2 cm caudal to the bregma. A small hole was then made in the superior sagittal sinus and a fine catheter inserted 2–3 mm towards the torcular Herophili. The craniotomy was sealed with dental cement. The arterial and cerebral venous (in triplicate) oxygen saturations were determined by reflection photometry during each estimation of cerebral blood flow, as was the haemoglobin concentration which was measured by a standard colorimetric technique.

The cerebral glucose uptake (CMR_{glu}) was calculated from the product of cerebral blood flow and the appropriate arteriovenous glucose concentration difference. Arterial and cerebral venous glucose concentrations, taken in triplicate, were measured by a standard enzymatic assay (Werner, Rey & Wielinger, 1970).

Carotid angiography. A gross assessment of the calibre of the internal carotid artery was made by carotid angiography. The contrast agent used was 2–4 ml. Conray 280, warmed at 37 °C before injection into the linguo-facial catheter. As contrast media can disrupt the blood-brain barrier (Jeppsson & Olin, 1975; Rapoport, Thomson & Bidinger, 1974) and increase cerebral blood flow (Grubb, Hernandez-Perez, Raichle & Phelps, 1974; Herrschaft, Gleim & Schmidt, 1974), the four animals in which angiography was performed were not used for any further measurements of cerebral blood flow.

Electroencephalography. The e.e.g. was recorded in all animals. In those that are illustrated later, the method described by Brierley, Brown, Excell & Meldrum (1969) was used. Seven epidural electrodes were inserted through the calvarium, 13 mm lateral to the sagittal suture, over each hemisphere. The electrodes were 10 mm apart in the sagittal plane. The electrodes were manufactured from silver wire, flamed to a small ball at the recording end, and coated with silver chloride. They were mounted through nylon screws and insulated externally with bone cement.

Osmotic opening of the blood-brain barrier. The tight junctions between adjacent endothelial cells of the cerebral capillaries and arterioles may be opened reversibly by the intracarotid infusions of hypertonic solutions (Rapoport, 1970; Rapoport, Hori & Klatzo, 1972). In the present investigations the blood-brain barrier was opened by the intracarotid administration of 7–10 ml. of a filtered, buffered urea solution (2 M: Ureaphil, Abbott). The hypertonic urea was infused over 15 sec and the pressure within the lingual artery catheter was maintained approximately 10 mmHg above the mean arterial pressure in each animal during the infusion. At no time was the common carotid artery clamped during this procedure

and measurements of cerebral blood flow and metabolism were made 5 min after the administration of the urea.

Although control experiments on the cerebrovascular effects of urea were not performed in the present study, previous investigations, under identical conditions, have shown that cerebral blood flow, cerebral oxygen consumption and cerebral glucose uptake are unaffected 5 min after the administration of urea (Pickard, Durity, Welsh, Langfitt, Harper & MacKenzie, 1977; MacKenzie, McCulloch, O'Keane, Pickard & Harper, 1976). In these earlier studies it was found that urea opened the blood-brain barrier to agents of widely differing molecular size, such as Evans blue albumin, penicillin G and noradrenaline.

RESULTS

The intracarotid infusion of 5-hydroxytryptamine (0·1 μg/kg.min) effected a marked constriction of the internal carotid artery. Carotid artery constriction was assessed angiographically in four baboons, and Pl. 1 demonstrates a typical example of this effect. A higher dose of 5-hydroxytryptamine (1·0 μg/kg.min) effected an even more marked vasoconstriction. This effect was sometimes so severe that no contrast medium at all could be visualized in the lumen of the internal carotid artery in some baboons. Complete occlusion of the internal carotid artery was never noted with the administration of the lower concentration of 5-hydroxytryptamine (0·1 μg/kg.min). The larger cerebral vessels, such as the pericallosal and middle cerebral arteries, appeared not to be affected by the intracarotid infusion of 5-hydroxytryptamine 0·1 or 1·0 μg/kg.min, but angiography provides only a gross assessment of the diameter of intracranial vessels and any changes must be marked in order to be meaningful.

Despite this obvious constriction of the internal carotid artery on the side of infusion, the ispilateral cerebral tissue perfusion was largely unaffected by the intracarotid infusion of 5-hydroxytryptamine (0·1 μg/kg.min) in seven baboons. Ipsilateral cerebral blood flow decreased slightly from 51 ± 2 to 48 ± 2 ml./100 g.min (mean ± S.E.), but this change was not statistically significant by Student's paired t test. Neither cerebral oxygen consumption nor glucose uptake was affected by the intracarotid infusion of 5-hydroxytryptamine by itself and these data, along with details of mean arterial pressure and arterial carbon dioxide tension, are summarized in Table 1. The base line values were based on between three and five measurements of cerebral blood flow at normocapnia, as were the values presented during the intracarotid 5-hydroxytryptamine infusion. The mean values in each animal before and during 5-hydroxytryptamine administration were analysed by Student's paired t test.

Following the intracarotid infusion of 5-hydroxytryptamine by itself, the blood-brain barrier was opened by the intracarotid infusion of 2 M-urea, as described in the Methods section, and the intracarotid infusion of

5-hydroxytryptamine was recommenced. This procedure was followed in only six of the baboons. Approximately three determinations of cerebral blood flow were made in each animal during the first 60 min following the intracarotid administration of hypertonic urea.

In contrast to the cerebral circulatory effects of 5-hydroxytryptamine by itself, the intracarotid infusion of 5-hydroxytryptamine 0·1 μg/kg.min following hypertonic urea effected a significant decrease in cerebral blood flow and in both indices of cerebral metabolism (Table 1) (Text-fig. 1) Neither 5-hydroxytryptamine alone, nor 5-hydroxytryptamine following hypertonic urea had any significant effect on mean arterial pressure or on the arterial carbon dioxide tension. Following the osmotic disruption of the blood-brain barrier, cerebral blood flow decreased and remained decreased in the 60 min after the administration of 5-hydroxytryptamine.

TABLE 1. Cerebral circulatory effects of intracarotid 5-hydroxytryptamine (5-HT, 0·1 μg/kg.min)

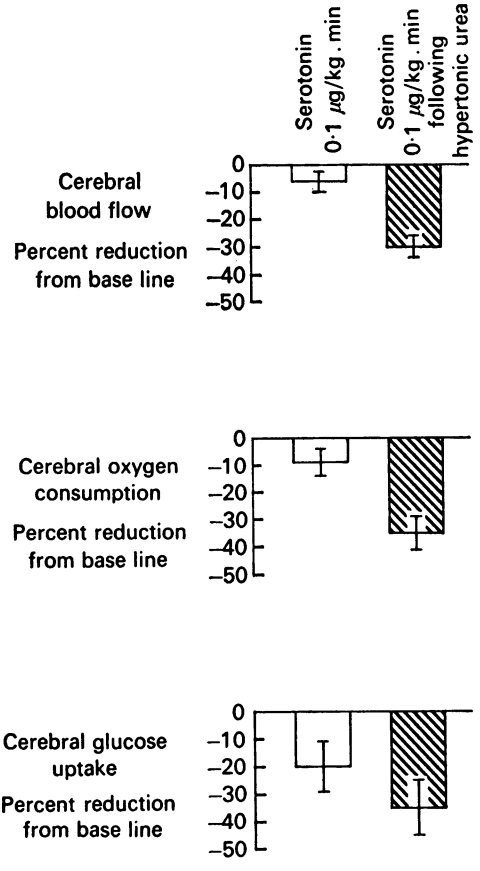
	Base line	5-HT	5-HT + urea
No. of animals ...	7	7	6
No. of observations ...	28	29	18
Cerebral blood flow (ml./100 g.min)	51 ± 2	48 ± 2	36 ± 2**
Cerebral oxygen consumtpion (ml./100 g.min)	3·23 ± 0·17	2·93 ± 0·16	2·09 ± 0·020**
Cerebral glucose uptake (mg/100 g.min)	4·55 ± 0·38	3·65 ± 0·43	2·97 ± 0·43*
Mean arterial pressure (mmHg)	93 ± 3	90 ± 4	90 ± 6
P_{a,CO_2} (mmHg)	40·0 ± 0·3	39·5 ± 0·3	39·7 ± 0·4

The figures presented are mean ± 1 S.E. of the mean. * = $P < 0·05$, ** = $P < 0·01$ by Student's paired t test between mean values in each animal.

After the discontinuation of the 5-hydroxytryptamine infusion, cerebral blood flow returned to base line levels very slowly; in two of the baboons cerebral blood flow was still markedly reduced 3 hr after the discontinuation of the 5-hydroxytryptamine.

Under phencyclidine/nitrous oxide anaesthesia the resting e.e.g. recording varies between continuous activity and a mild suppression-burst type of activity. The intracarotid infusion of hypertonic urea, by itself, did not appear to effect the e.e.g. a comparison being made in Text-figs. 2*A* and *B*. Likewise, the intracarotid infusion of 5-hydroxytryptamine, by itself, did not appear to effect the electroencephalogram. However, when 5-hydroxytryptamine was infused after the intracarotid administration of

hypertonic urea the periods of suppression tended to be isoelectric, and the amplitude of the bursts was reduced, indicating a deeper stage of electrocortical activity. This effect can be compared in Text-fig. 3*A* and *B*.



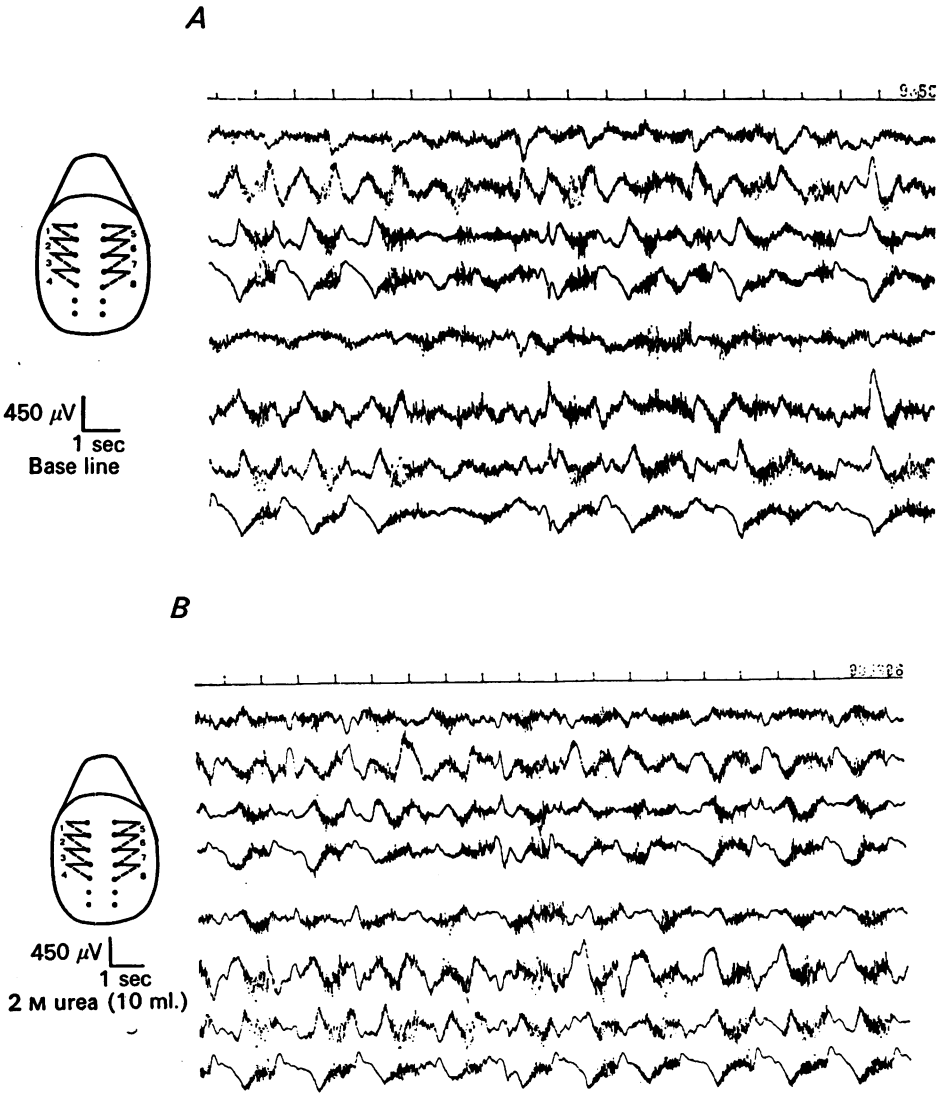
Text-fig. 1. Cerebral circulatory and metabolic effects of intra-carotid 5-hydroxytryptamine (0·1 μg/kg.min) before and after (cross-hatched) osmotic disruption of the blood-brain barrier.

DISCUSSION

The intracarotid infusion of 5-hydroxytryptamine 0·1 μg/kg.min effected a marked constriction of the internal carotid artery, as assessed angiographically. In preliminary experiments we noted that the intracarotid infusion of 1·0 μg/kg.min could, in some baboons, effect such a severe constriction that the lumen of the internal carotid artery was completely obliterated. In agreement with the present investigation, a 5-hydroxytryptamine-induced selective vasoconstriction of the internal

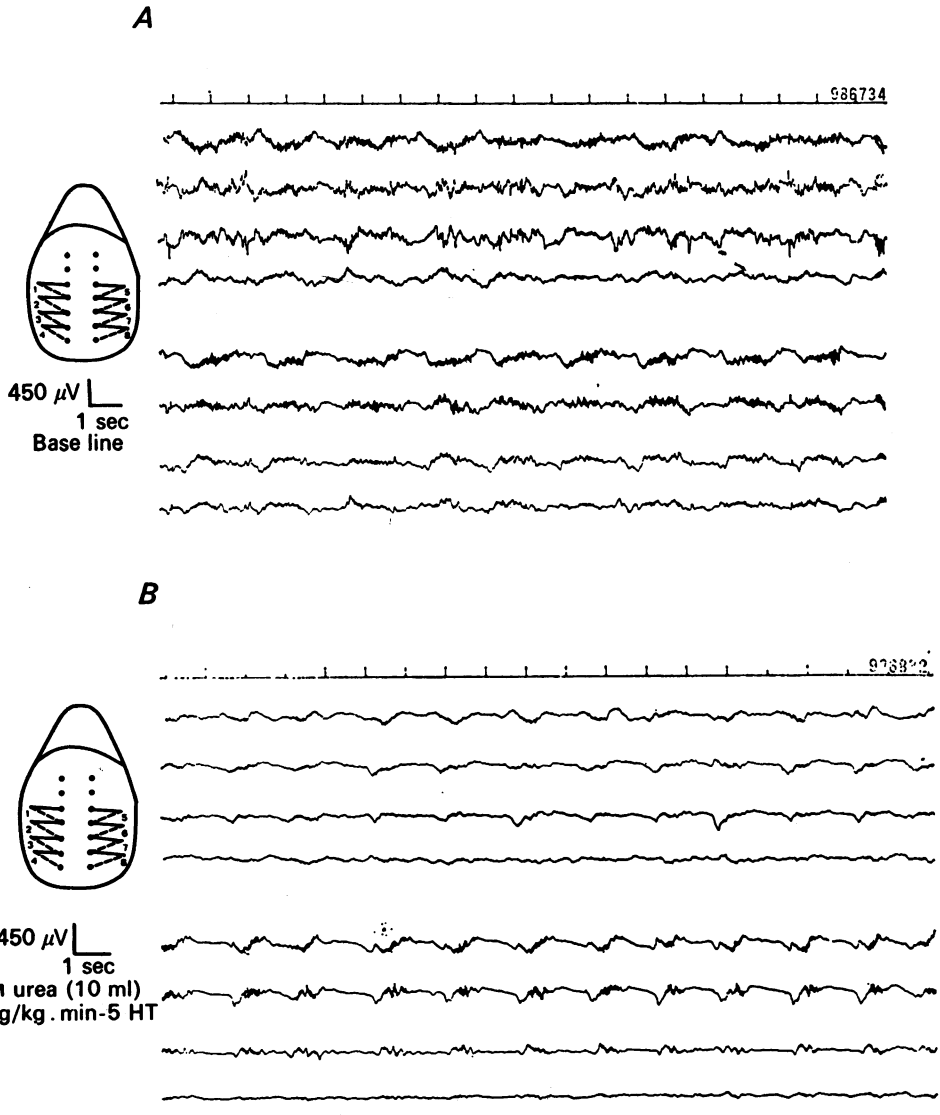
carotid artery has been noted in earlier studies following the intra-arterial administration of this amine (Grimson, Robinson, Danford, Tindall & Greenfield, 1969; Deshmukh & Harper, 1973).

Despite the pronounced vasoconstriction of the arterial inflow to the brain, cerebral tissue perfusion was not affected by the intracarotid



Text-fig. 2. Bipolar e.e.g. recordings. The traces are numbered from top to bottom (1–4, left side; 5–8, right side). *A*, base line; *B*, in the same animal, 5 min after the left intra-carotid infusion of 10 ml. hypertonic urea (2 M).

infusion of 5-hydroxytryptamine 0·1 μg/kg.min by istelf. There are two implications that arise from these observations: first, that the distal cerebral arterioles did not react to the systemic administration of the agent and, secondly, that downstream mechanisms compensated for the



Text-fig. 3. Bipolar e.e.g. records. Different animal from that in Text-fig. 2 but numbering the same. *A*, base line; *B*, 5 min after the intra-carotid infusion of 10 ml. hypertonic urea (2 M) and the subsequent infusion of 5-hydroxytryptamine (0·1 μg/kg.min).

reduction of arterial inflow so as to maintain the constancy of cerebral blood flow through the circle of Willis or other channels.

The non-reactivity of the downstream arterioles to the systemic administration of 5-hydroxytryptamine could well be explained by the existence of blood-brain barrier mechanisms to this amine. The entry of 5-hydroxytryptamine from blood into brain is extremely limited (Oldendorf, 1971) and it is known that enzymatic barrier mechanisms exist to both 5-hydroxytryptamine and 5-hydroxytryptamine precursors at the level of the cerebral capillary endothelial cells (Bertler, Falck, Owman & Rosengrenn, 1966). Although a systematic investigation has yet to be carried out, the available evidence would indicate that the intraparenchymal and pial arterioles are protected by a endothelial barrier, whilst large extracerebral vessels, such as the internal carotid are not (Edvinsson & MacKenzie, 1976). If confirmed, these functional and morphological differences would explain the lack of effect of systemic 5-hydroxytryptamine on cerebral blood flow, compared with its marked effect on the calibre of the internal carotid artery into which it was infused.

Our current findings confirm those of Rapela & Martin (1975) who have shown that the administration of 5-hydroxytryptamine (in comparable concentrations to those of the present investigation) can increase markedly the tone of the internal carotid artery, whilst leaving cerebral tissue perfusion unchanged. Internal carotid artery tone was assessed as the pressure difference between the common carotid artery and the circle of Willis. Using a higher dose of 5-hydroxytryptamine, Deshmukh & Harper (1973) have demonstrated a reduction in internal carotid artery blood flow of 57 % and a concomitant reduction in cerebral tissue perfusion of only 17 % at normocapnia. As the majority of the previous studies on the relationship between 5-hydroxytryptamine and the cerebral circulation have used electromagnetic flowmetry on the internal carotid artery as an index of cerebral tissue perfusion, it is probable that such studies have overemphasized the reduction in cerebral tissue perfusion that would be associated with the intra-arterial administration of the amine (Karlsberg, Elliot & Adams, 1963; Lowe & Gilboe, 1973; Welch, Hashi & Meyer, 1973; Welch, Spira, Knowles & Lance, 1974; White, Heaton & Denton, 1971).

Two further factors would complicate any investigation on the cerebral circulatory effects of 5-hydroxytryptamine, and could explain some of the discrepancies in the literature. The first factor is that the pharmacodynamic characteristic of the 5-hydroxytryptamine receptor is markedly different in the cerebral vessel wall, when compared to extracranial arteries (Edvinsson & Hardebo, 1976; Edvinsson, Hardebo & Owman, 1977). The administration of 5-hydroxytryptamine increases external carotid artery blood flow and increases perfusion in extracranial tissues such as the

temporal artery (Deshmukh & Harper, 1973; Grimson *et al.* 1969; Vidrio & Hong, 1976). Unless steps are taken to adequately isolate the extracranial from the cerebral circulation, the opposite effects of 5-hydroxytryptamine on the two dissimilar vascular beds will confuse the final interpretation. The baboon, compared to most species, has few anastomoses between the cerebral and extracranial circulations, and in the current study the added precautions of ligating the branches of the external carotid artery and removing the extracranial tissues from the calvarium were taken. The second factor that could complicate the effects of 5-hydroxytryptamine on the cerebral circulation is the resting tone of the cerebral arterioles. In peripheral vascular beds arteriolar tone determines the overall response to 5-hydroxytryptamine (Haddy, Gordon & Emanuel, 1959), and the relevance of this phenomenon to the cerebral circulation has been discussed elsewhere (Harper & MacKenzie, 1977).

On the assumption that barrier mechanisms played a significant role in determining the cerebrovascular response to systemic 5-hydroxytryptamine, the intracarotid infusion of this agent was studied following transient osmotic disruption of the blood-brain barrier. A decrease in both cerebral oxygen and glucose consumption was observed along with the decrease in cerebral blood flow, and it is pertinent to ask the question as to which effect preceded the other. Cerebral blood flow can be reduced by 30% during, for example, hypocapnia but without any simultaneous reduction in cerebral metabolism (Kety & Schmidt, 1948). On the other hand, the intimate link between changes in blood flow and the underlying neuronal metabolism has long been recognized, and recently this coupling has been demonstrated directly (Raichle, Grubb, Mokhtar, Gado, Eichling & Ter-Pogossian, 1976). Accordingly, it would appear improbable that the 5-hydroxytryptamine-induced reduction in cerebral metabolism was secondary to an effect on cerebral blood flow. The observation that the *direct* effect of 5-hydroxytryptamine on the smaller pial arterioles *in vivo* is dilatatory, and not constrictory, supports this contention (Harper & MacKenzie, 1977).

It then becomes necessary to ask the question as to whether the 5-hydroxytryptamine effects on cerebral metabolism are direct, or whether the metabolic effects were themselves secondary to electrocortical changes. For instance, another biogenic, vasoactive amine, noradrenaline, can stimulate oxygen and glucose consumption directly, via an action on cyclic-3′,5′-adenosine monophosphate in brain tissue (Kakiuchi & Rall, 1968*a*,*b*; Klainer, Chi, Freidberg, Rall & Sutherland, 1962). Noradrenaline, though classified usually as a vasco-constrictor agent, can increase cerebral blood flow, putatively through an effect on cerebral metabolism, when it gains access to the cerebral interstitial fluid (MacKenzie, McCulloch,

O'Keane, Pickard & Harper, 1976; MacKenzie, McCulloch & Harper, 1976). However, the effects of 5-hydroxytryptamine on cerebral adenyl cyclase *in vitro* are similar to the effects of noradrenaline, namely a stimulated production of cyclic-3′,5′-adenosine monophosphate (Kakiuchi & Rall, 1968*a*,*b*). Thus, the direct action of 5-hydroxytryptamine on the mechanisms which control intermediary metabolism is contrary to the decrease in cerebral oxygen and glucose consumption observed in the present study. Accordingly, it must be considered that the primary action of 5-hydroxytryptamine, after it has bypassed the blood-brain barrier, is on neuronal activity with consequent effects on brain metabolism and blood flow.

Our electroencephalography results are consistent with, though less dramatic than, those of Domer & Longo (1962) who noted that the injection of the 5-hydroxytryptamine precursor, 5-hydroxytryptophan, which can readily permeate the blood-brain barrier, resulted in a practically isoelectric tracing. Both Domer & Longo (1962) and Monnier (1960) suggested that the changes they observed with the administration of agents, such that the brain levels of 5-hydroxytryptamine were elevated, were due to a depression of the reticular system. The brain stem systems that contain 5-hydroxytryptamine are concerned closely with both the electrocortical and behavioural aspects of sleep, as reviewed by Jouvet (1972).

In conclusion, a significant decrease in cerebral blood flow occurs when 5-hydroxytryptamine gains access to the cerebral interstitial fluid. Though the techniques of this study do not allow a definitive statement to be made, it is inferred that this decrease in cerebral blood flow is secondary to actions of 5-hydroxytryptamine on cortical activity.

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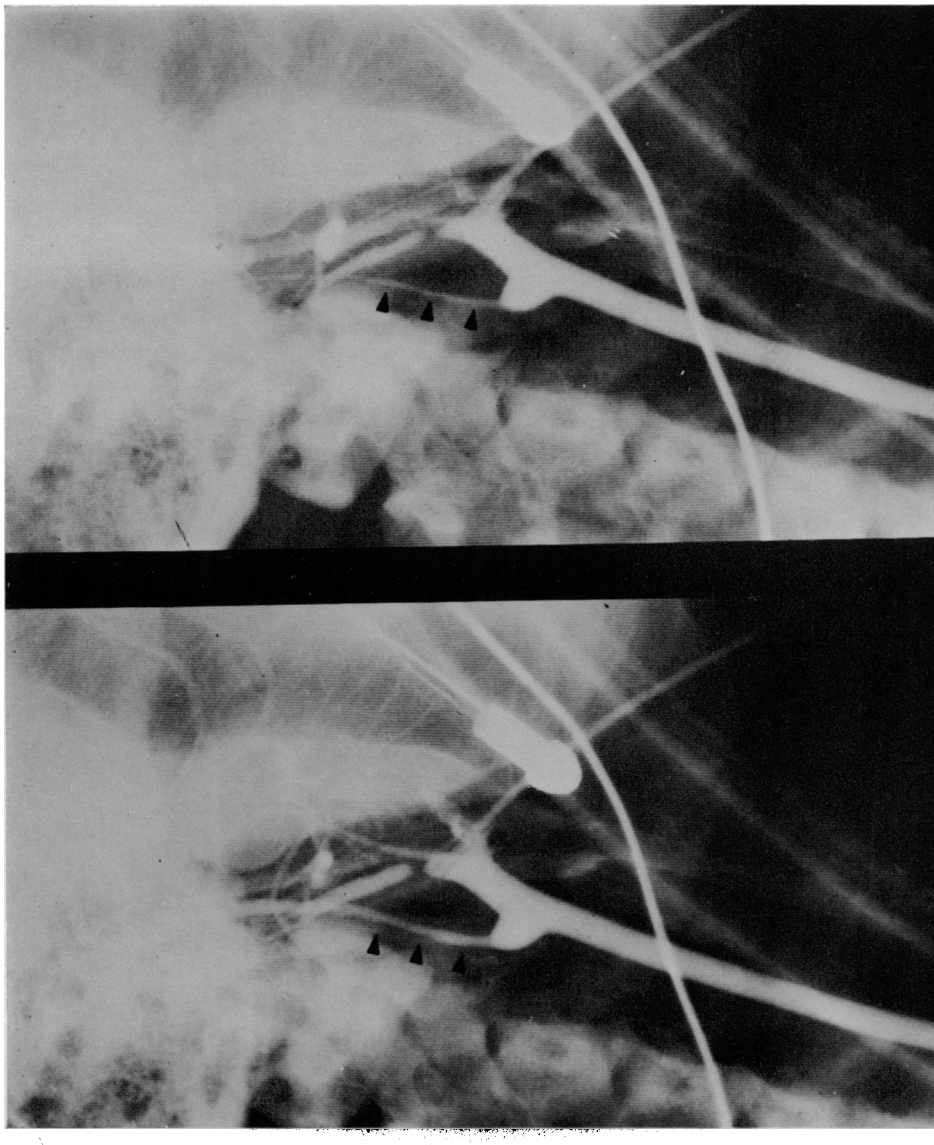

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EXPLANATION OF PLATE

The effect of the intracarotid infusion of 5-hydroxytryptamine (0·1 μg/kg.min) on internal carotid artery calibre. The lower angiogram shows the vessel in the control state, while the upper angiogram shows the vessel during the 5-hydroxytryptamine infusion. The arrowheads indicate the extracranial course of the artery. The major branches of the external carotid artery have been ligated.