Cerebrovascular Response to Infused 5-Hydroxytryptamine in the Baboon

Part 1. 5-Hydroxytryptamine Infusion

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SUMMARY Cerebral blood flow was measured in 17 baboons before and during infusion of 5-hydroxytryptamine (5-HT) into the internal carotid artery. The mean values for total cerebral blood flow, grey matter flow, and white matter flow before 5-HT infusion were 40.8, 59.2, and 12.7 ml/min/100 gm of tissue, respectively. There was no significant alteration in total blood flow or flow through grey matter when 5-HT was infused at dosages ranging from 0.5 to 10.0 \( \mu \)g/kg/min. A small but significant decrease in white matter blood flow was recorded when 5-HT was infused at a rate exceeding 2.5 \( \mu \)g/kg/min. The study indicates that in vivo, with the \(^{133}\)xenon clearance method, intra-arterial infusion of 5-HT does not significantly alter cerebral blood flow.

THE PATHOGENESIS OF cerebral arterial spasm in migraine and subarachnoid hemorrhage has been related to a variety of naturally occurring substances. It has been shown that blood, hemolyzed serum, platelets, nor-adrenaline, certain prostaglandins, and serotonin (5-hydroxytryptamine) induce spasm when applied topically to cerebral vessels. The role of 5-hydroxytryptamine (5-HT) as a spasmogen has been studied extensively. Its effects differ depending on the route of administration. While application of 5-HT to the adventitial surface of cerebral vessels consistently produces constriction, intra-arterial administration has not produced the same results. It has been suggested that 5-HT is metabolized by monoamine oxidase in endothelial cells, and its entry into these cells is impeded at the luminal surface. This blood-brain barrier may account for the lack of constriction when 5-HT is administered via the intra-arterial route. Furthermore, some of the reported effects of intra-arterial administration were assessed by methods other than isotope clearance techniques which do not necessarily correlate with cerebral perfusion. There are few studies on the effect of intra-arterial 5-HT on cerebral blood flow using the \(^{133}\)xenon clearance method, and dose response curves have not been fully documented. In part 1 of this study, we have measured the effect of intracarotid infusion of 5-HT at various concentrations (0.5 to 10.0 \( \mu \)g/kg/min) on cerebral blood flow in baboons using the \(^{133}\)xenon clearance technique.

Methods

Seventeen adult baboons (Papio ursinus), weighing 10 to 20 kg, were sedated with ketamine hydrochloride (Ketalar, Parke Davis) by intramuscular injection, and anesthesia was induced by intravenous pentobarbitone sodium, 5 mg/kg (Nembutal, Abbott Laboratories). Each animal was intubated and ventilated mechanically with a mixture of \( \text{N}_2\text{O} \) and \( \text{O}_2 \) (2:1). Anesthesia was maintained with intermittent small doses of pentobarbitone sodium. A catheter was inserted into the femoral artery to permit continuous measurement of mean and pulsatile blood pressure with a Statham P23AA transducer and to provide access for arterial blood gas sampling. The mean blood pressure was maintained within the limits of autoregulation of cerebral blood flow. Blood gas measurements were made prior to each cerebral blood flow measurement on an Instrumentation Laboratories 313 blood gas analyzer. End-expiratory \( \text{CO}_2 \) percentage was monitored continuously with a Goddart Capnograph. The bladder was catheterized and remained empty throughout the experiment.

Cerebral Blood Flow Measurements

The right lingual artery was cannulated with a double lumen catheter which was inserted until its tip lay at the carotid bifurcation but not within the internal carotid artery. This catheter was used to permit infusion of 5-HT independently of \(^{133}\)xenon. All other branches of the external carotid artery were ligated. Extracranial flow was further eliminated by turning a scalp and temporalis muscle flap down over the right frontoparietal area. A highly collimated scintillation detector, fitted with a 5 cm \( \times \) 2 mm sodium iodide crystal, was positioned over the exposed bone in this area. The surrounding scalp and orbits were shielded with a lead screen. Cerebral blood flow was thus measured by determining the cerebral clearance rate of a 30 to 50 \( \mu \)Ci bolus of \(^{133}\)xenon, injected into the internal carotid artery. The uptake and clearance curves from the injected \(^{133}\)xenon were recorded digitally by means of a Nuclear Enterprises Data Logging System. The data were analyzed manually and by a computer into two compartments representing flow through grey and white matter. Total cerebral blood flow was determined from grey and white flow values, assuming a grey:white ratio of 6:4. Throughout the experiments the arterial \( \text{Pco}_2, \text{Po}_2, \) and \( \text{pH} \) values were monitored and maintained within physiological limits at 1,660 m (altitude in Johannesburg).

After a 60-minute standardization period control cerebral blood flow was measured. The 5-HT was then infused at concentrations from 0.5 to 10.0 \( \mu \)g/kg/min for a 10-minute period prior to measuring cerebral blood flow. Control measurements were repeated at intervals throughout the experiment, allowing a 30-minute period to elapse after 5-HT infusion had been discontinued.

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Results

Intracarotid infusion of 5-HT produced no significant alteration in cerebral blood flow in these experiments. The effect of intra-arterial administration of 5-HT on hemisphere blood flow should reflect changes in flow to cerebral tissue as a whole. The method describes reflects total cerebral blood flow.

The mean control values for total cerebral blood flow (F), grey matter flow (fg), and white matter flow (fw) were 40.8, 59.2, and 12.7 ml/min/100 gm of tissue, respectively. The corresponding values of F, fg, and fw with infusion of 5-HT are shown in figures 1, 2, and 3. There was no significant change in F or fg during infusion of 5-HT at any concentration, nor was there any distinct trend of change in flow. White matter flow (fig. 3) decreased slightly at all concentrations of infused 5-HT but was significant only at concentrations exceeding 2.5 μg/kg/min (P < 0.025).

Throughout the experiment the arterial Pco₂ was maintained constant in each animal. The mean arterial blood pressure was maintained within the limits of autoregulation, and in no individual measurement was the mean blood pressure outside the range of 80 to 150 mm Hg.

Apart from a minor decrease in blood flow through white matter, 5-HT produced no change in total flow through grey matter. These results may indicate slight redistribution of flow from white to grey matter but do not support some of the previous reports of reduction in total blood flow, as measured by other techniques.

Discussion

In the present study, excepting for a minor decrease in blood flow through white matter, intra-arterial infusion of 5-HT produced no changes in total flow or flow through grey matter. These results may indicate slight redistribution of flow from white to grey matter but do not support some of the previous reports of reduction in total blood flow, as measured by other techniques.

The effect of 5-HT on the cerebral vasculature has been widely studied with a variety of methods, but reports on its effect on cerebral blood flow are conflicting. In vitro experiments have clearly demonstrated that 5-HT produces constriction of cerebral arteries as well as peripheral vessels. It has also been shown that cerebral vessels are more sensitive to 5-HT than to noradrenaline, and De La Lande has demonstrated that 5-HT enhances the constrictor response to noradrenaline. Direct observations of cere-
bral vessels after topical application of 5-HT in vivo have revealed constriction.\textsuperscript{1,2} Simone\textsuperscript{a} and Chow,\textsuperscript{2} using angiographic techniques, reported constriction after application of 5-HT to large cerebral vessels. In isolated brains of dogs\textsuperscript{2} and monkeys,\textsuperscript{2} vasoconstriction was produced by intra-arterial infusion of 5-HT. With electromagnetic flowmeters Welch et al.\textsuperscript{3,4} demonstrated decreased flow through external and internal carotid arteries in primates during intra-arterial 5-HT infusion. Using a similar technique, Grimson et al.\textsuperscript{5} reported a 58\% decrease in internal carotid flow while external carotid flow increased. Applying a strain gauge method to the internal carotid artery, Brawley\textsuperscript{6} reported constriction. However, Swank and Hissen\textsuperscript{7} using electromagnetic flowmeters, demonstrated an increase in flow through the common carotid artery during 5-HT infusion.

Deshmuck and Harper\textsuperscript{8} combined flowmeter studies with cerebral perfusion studies using \textit{in situ} xenon; they demonstrated a decrease in internal carotid flow and an increase in external carotid flow while cerebral perfusion remained unchanged. In a later paper\textsuperscript{9} the same authors demonstrated that cerebral perfusion diminished by 17\% when 5-HT was infused at the rate of 1 \(\mu\)g/kg/min. Other reports on the effect of 5-HT on cerebral perfusion in vivo using isotope clearance techniques have been variable. Yamamoto\textsuperscript{10} demonstrated a 10\% fall in cerebral blood flow in dogs. Olesen\textsuperscript{11} studied the effect of intra-arterial infusion of 5-HT in human subjects and found no significant decrease in total cerebral blood flow. Rapella\textsuperscript{12,13} demonstrated constriction of extraparenchymal vessels in dogs but no decrease in cerebral perfusion. Ekström-Jodal et al.\textsuperscript{4} found a decreased blood flow in dogs using krypton. Rosendorff and Cranston\textsuperscript{14} measured local hypothalamic blood flow in conscious rabbits and found a dose-related increase in blood flow.

It is apparent that when CBF is evaluated angiographically, with flowmeters, by observing changes in caliber of major vessels in vivo, and in vitro, the effects of 5-HT on cerebral vessels are constrictor in nature. However, when cerebral perfusion is measured in vivo with isotope clearance techniques, the reported changes in cerebral blood flow with infusion of 5-HT fail to reveal a clear-cut response, with most studies showing little change in cerebral blood flow. In the majority of these experiments, only a single dose of infused 5-HT was evaluated with doses ranging from 24 \(\text{ng/kg/min} \) to 15 \(\mu\)g/kg/min. It is difficult, therefore, to draw meaningful conclusions from this wide array of data. In the series of experiments reported by Deshmuck and Harper,\textsuperscript{8} 5-HT concentration was varied from 0.5 to 2.5 \(\mu\)g/kg/min, and no significant change in cerebral blood flow was reported. This study, however, was carried out on a small series of animals.

In the present study the effects of 5-HT on CBF have been extensively examined. Our data indicate that in the baboon there is no significant alteration in cerebral blood flow when 5-HT is infused over the range 0.5 to 10 \(\mu\)g/kg/min. These findings are somewhat at variance with the results obtained by those authors who have studied the effects of 5-HT by methods other than isotope clearance and by administration of 5-HT other than intra-arterially. There are several explanations for these conflicting results.

The presence of a blood-brain barrier to 5-HT was reported by Hardebo et al.\textsuperscript{15} who point out that 5-HT is mechanically prevented from passing through the luminal surface and that endothelial cells possess monoamine oxidase which breaks down 5-HT. This may account for the lack of response to infused 5-HT reported here and by others.\textsuperscript{16,17}

This argument does not apply to flowmeter studies in which 5-HT has been infused intra-arterially. The flowmeter can accurately determine the rate of flow within the vessel under study. However, there are limitations to the technique, which may not provide an accurate measure of total cerebral perfusion. Flow in a single vessel is not necessarily representative of central perfusion since there are major anastomotic channels in the circle of Willis and the leptomeningeal circulation which may divert blood to other areas independent of recorded changes of flow within the artery under study. Also, despite the well-separated internal and external circulations in the primate, a significant proportion of blood destined for the orbit and surrounding structures is carried in the internal carotid artery, and changes of blood flow in this extracerebral compartment will influence flow in the internal carotid artery.\textsuperscript{16} Evidence from the studies of Deshmuck and Harper\textsuperscript{8} have shown that major changes in carotid blood flow as measured by a flowmeter may occur without any simultaneous, detectable changes in cerebral perfusion. It is thus evident that data obtained from flowmeter studies do not necessarily reflect changes in cerebral perfusion. This observation may well be a major factor in explaining the discrepant findings between flowmeter and cerebral perfusion studies.

A further possibility is that 5-HT may produce constriction of major vessels but that while autoregulation is intact, the smaller arteries dilate to maintain constant perfusion. This was confirmed by Rapella and Martin.\textsuperscript{18}

It has been postulated that 5-HT may be one of the most important factors in the pathogenesis of cerebral arterial spasm in migraine and subarachnoid hemorrhage.\textsuperscript{19-21} Despite these reports the lack of effect of intra-arterially administered 5-HT, reported here and by other workers,\textsuperscript{8,22-24} suggests that the major cerebral blood flow changes described in migraine\textsuperscript{21,22} and subarachnoid hemorrhage\textsuperscript{24,25} cannot be attributed to 5-HT arriving on the endothelial side of the receptor. This possibility may be accounted for by the rapid removal of 5-HT by uptake mechanisms and metabolism within the endothelial cell by monoamine oxidase.\textsuperscript{26} It is possible that in certain pathological states this metabolism may be disordered, thereby allowing higher concentrations of intra-arterial 5-HT to reach receptors on membranes of smooth muscle cells.

\textbf{References}

CBF RESPONSE TO 5-HT IN BABOON/Mendelow et al.

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