Cerebrovascular Response to Infused 5-Hydroxytryptamine in the Baboon

Part 2. 5-Hydroxytryptamine Infusion in Estrogen and Progesterone Treated Animals

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SUMMARY The effect of intracarotid infusion of 5-hydroxytryptamine (5-HT) on cerebral blood flow was studied in five female baboons 7 days after intramuscular injection of slow release estrogen and progesterone. The control values for total cerebral blood flow, grey matter flow, and white matter flow were 38.9, 57.5 and 11.0 ml/min/100 gm of tissue respectively. There was a statistically significant decrease in total, grey and white matter blood flow during infusion of 5-HT at dosages ranging from 0.5 to 10.0 µg/kg/min. The study indicates that in female baboons pretreated with estrogen and progesterone, intracarotid infusion of 5-HT produces a dose dependent decrease in cerebral blood flow, which did not occur in control animals.

Method

Five adult female baboons (Papio ursinus) weighing 10-20 kg were injected intramuscularly with a depot preparation of estrogen (Oestradiol Valerate: 2.5 mgm, Schering) and progesterone (Medroxy-Progesterone Acetate: 25 mgm, Upjohn) 7 days prior to each experiment. These dosages were calculated to be equivalent on a weight for weight basis to those given to humans for contraception. On the day of the experiment the animal was anesthetized and prepared using methods described previously. This permitted continuous monitoring of mean and pulsatile blood pressure, expiratory CO₂, with blood gas analysis, and cerebral blood flow measurements using the ¹⁴C-xenon clearance technique. Infusions of 5-HT were made via the internal carotid artery in dosages ranging from 0.5 to 10.0 µg/kg/min. Cerebral blood flow was measured at least 10 minutes after commencing the infusion at each dosage. Control measurements were repeated at intervals during the experiment, allowing a 30 minute period to elapse after the 5-HT infusion had been discontinued.

Results

The effect of intracarotid infusion of 5-HT on cerebral blood flow in animals pretreated with estrogen and progesterone differed dramatically from the effect in normal animals reported in Part 1. While control levels of cerebral blood flow were unchanged, a marked decrease in cerebral blood flow occurred at all dosages of infused 5-HT in the pretreated animals. The mean control values for total cerebral blood flow (F), grey matter blood flow (fg), and white matter blood flow (fw) were 38.9, 57.5 and 11.0 ml/min/100 gm of tissue respectively. The mean values (± 1 sd) of F, fg and fw with infusion of 5-HT are shown in figures 1, 2 and 3. There was a decrease in F, fg and fw at all concentrations of infused 5-HT which was most pronounced at the highest dosage (10.0 µg/kg/min). The mean values of flow at all levels of infused 5-HT were significantly different from the baseline values (P < 0.05, Student’s paired t test). The PaCO₂ was maintained within physiological limits at this altitude (1660 meters). The mean arterial blood pressure was maintained within the limits of autoregulation.

Discussion

The results of these experiments indicate that intracarotid infusion of 5-HT produces a marked decrease in cerebral blood flow in female baboons pretreated with estrogen and progesterone in contrast to the control situation where 5-HT produced no change.

Migraine headache is thought to be due to cerebrovascular dilatation, and is frequently preceded by a prodromal phase during which cerebrovascular constriction occurs and results in transient focal neurological symptoms and signs on an ischemic basis. During this phase of cerebrovascular constriction, decreased cerebral blood flow has been demonstrated by O’Brien and Skinhøj. The mechanism by which decreased cerebral blood flow is produced has not been fully elucidated. Anthony, Hinterberger and Lance have shown that platelet 5-HT levels are decreased during the headache phase of migraine. Similar findings were reported by Cumings. Sjaastad has reviewed the role of 5-HT in migraine and has pointed out that a change in the metabolism of 5-HT may be the impor-
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Figure 1. The mean total cerebral blood flow (ml/min/100g of tissue) is shown with the doses of 5-HT in female baboons pretreated with estrogen and progesterone. The vertical lines represent 1 standard deviation. Decreased flow was observed at all dosages of infused 5-HT (Student's t test at each dosage from 0.5 to 10.0 µg/kg/min respectively: P < 0.0025, P < 0.025, P < 0.025, P < 0.0125, P < 0.0005).

Figure 2. The mean grey matter blood flow (ml/min/100g of tissue) is shown with the doses of 5-HT in female baboons pretreated with estrogen and progesterone. The vertical lines represent 1 standard deviation. Decreased flow was observed at all dosages of infused 5-HT (Student's paired t test at each dosage from 0.5 to 10.0 µg/kg/min respectively: P < 0.01, P < 0.05, P < 0.025, P < 0.025, P < 0.0005).

Figure 3. The mean white matter blood flow (ml/min/100g of tissue) is shown with the doses of 5-HT in female baboons pretreated with estrogen and progesterone. The vertical lines represent 1 standard deviation. Decreased flow was significant at dosages exceeding 1.0 µg/kg/min. (Student's paired t test at each dosage from 0.5 to 10.0 µg/kg/min respectively: N.S., P = 0.05, P < 0.025, P < 0.01, P < 0.025).

Tant factor. There are many other factors which have been implicated in the pathogenesis of migraine including inherited abnormalities, trigger factors, and local abnormalities. Among the trigger factors, hormonal changes are recognized as commonly precipitating an attack. In particular, pregnancy, premenstrual tension, and use of the contraceptive pill are known to be of significance. Epstein has reported abnormally high levels of estrogen and progesterone throughout most of the menstrual cycle in females with menstrually linked migraine. It is possible that the observed susceptibility of patients with elevated sex steroid levels to more frequent migraine attacks may be related to effects of these substances on 5-HT metabolism, producing an enhanced vascular sensitivity to serotonin (5-HT). A similar argument may apply in the vascular spasm reported in subarachnoid hemorrhage where decreased cerebral perfusion has been well documented.19, 14

The role of 5-HT in subarachnoid hemorrhage has been shown to be one of several important factors responsible for arterial spasm.13-17 As in migraine, spasm has been reported to occur more frequently in young females.18 It is possible that increased sensitivity to 5-HT in these patients with elevated levels of estrogen and progesterone may be of importance in the genesis of vascular spasm.

The effect of 5-HT on cerebral arteries is controversial. In vitro studies have indicated that 5-HT produces constriction of larger cerebral arteries.19, 20 In vivo studies, using the isotope clearance technique,4, 31, 32 and cerebral venous outflow techniques,33 have shown that intracarotid infusions of 5-HT do not decrease cerebral perfusion although constriction of extraparenchymal vessels may take place. There are two possible explanations. Firstly, constriction of extraparenchymal large vessels may result in autoregulatory dilatation of the smaller intraparenchymal resistance arteries.34 Secondly, 5-HT arriving on the endothelial surface of the resistance vessels may be prevented from reaching receptor sites on smooth muscle cells by metabolism with monoamine oxidase.35 Enzyme inactivation of 5-HT may take place in the endothelial cell36, 37 or in arterial smooth muscle itself.38

The explanation for the decreased cerebral perfusion in the estrogen and progesterone treated animals may be related to a decrease in the ability of cerebral vessels to inactivate 5-HT. There is evidence that steroid hormones influence 5-HT metabolism in arterial tissue,39 as well as other tissues.40, 41

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and that they inhibit monoamine oxidase activity.\textsuperscript{17, 18} Furthermore, steroid hormones inhibit extraneuronal uptake of catecholamines.\textsuperscript{29-42} As 5-HT is accumulated in arterial tissue in a manner very similar to noradrenaline,\textsuperscript{27} we suggest that the steroid hormones, estrogen and progesterone, inhibit metabolic inactivation, which normally protects the cerebral vasculature from circulating 5-HT. Previous work in our laboratory has shown that corticosterone has a similar effect,\textsuperscript{43} and that noradrenaline is likewise inactivated by avid extraneuronal uptake mechanisms.\textsuperscript{44}

The clinical implications in pathological states of decreased cerebral perfusion, such as migraine and subarachnoid hemorrhage, are that elevated levels of steroid hormones may interfere with the blood brain barrier to 5-HT as well as extraneuronal uptake processes. This may enhance the effect of intravascular serotonin on arterial smooth muscle and thereby play a role in the pathogenesis of cerebral vasospasm.

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