Effects of Intrahypothalamic and Intraventricular Norepinephrine and 5-Hydroxytryptamine on Hypothalamic Blood Flow in the Conscious Rabbit

By Clive Rosendorff and William I. Cranston

ABSTRACT

Hypothalamic blood flow (HBF) was measured in the conscious rabbit using a $^{133}$Xe clearance technique. The effects of intrahypothalamic norepinephrine (NE) and 5-hydroxytryptamine (5-HT) were determined by adding these compounds to the $^{133}$Xe-in-saline injectate, in varying concentrations. NE produced dose-dependent changes in flow; 1 $\mu$g/injection caused a mean increase in HBF of 55%, while doses of 10, 20, 40 and 200 $\mu$g/injection reduced HBF by mean values of 26%, 17%, 20% and 29% respectively. The constrictor effect of NE 40 $\mu$g/injection was prevented by the addition of phenoxybenzamine 50 $\mu$g/injection. Intrahypothalamic injections of 5-HT (20, 40 and 80 $\mu$g/injection) caused increases in mean HBF of 24%, 54% and 69% respectively. Injections of NE into the lateral cerebral ventricles caused an increase in HBF; 5-HT produced a variable response, but mean values for HBF tended to be lower after the injection. There were no changes in mean arterial blood pressure or arterial $P_{CO_2}$. It is concluded that NE and 5-HT have an action on hypothalamic resistance vessels when applied from the adventitial side, and that, in the case of NE, the response is dose dependent, and the vasoconstrictor effects may be mediated by alpha receptors in hypothalamic vessels.

KEY WORDS: $^{133}$Xe clearance method; brain blood flow; cerebral circulation; cerebrovascular physiology; indoleamines; nervous control of cerebral vessels; adrenergic innervation; alpha-receptor activation; catecholamines

Although elsewhere in the body norepinephrine (NE) and 5-hydroxytryptamine (5-HT) have profound effects on blood vessels, their action on total cerebral blood flow is controversial. In the dog, NE infused intravenously causes cerebral vasconstriction (1), and in man it produces either no change or a small fall in cerebral blood flow (2-4). The response to 5-HT has been reported as vasoconstrictor (5, 6) and vasodilator (7). There are difficulties in the interpretation of these results because the intravenous administration of vasoactive drugs which alter mean arterial blood pressure might affect cerebral vessels via autoregulation of cerebrovascular tone in response to the blood pressure change rather than by any direct action on the cerebral vasculature. In addition, since in many of these studies only total cerebral blood flow was studied, any local flow changes in the brain might have been missed.

The role of a neural mechanism in the control of cerebral blood flow is a question of considerable controversy (8, 9). There is, however, good evidence that in various species, including the rabbit, there is a rich...
adrenergic innervation of the cerebrovascular system (10, 11) situated in nerve plexuses on the adventitial side of the media. This subadventitial location of the adrenergic plexus, as well as the responsiveness of isolated blood vessels to externally applied NE and 5-HT (12-14), would suggest that parenchymal vessels in the brain might respond to these drugs applied externally.

For these reasons we have examined the effects of local application of these amines on local cerebral blood flow in a conscious animal. The method used in this study for the measurement of local blood flow is based on the rate of clearance of locally injected \(^{133}\)Xe; this technique allows for the addition of NE or 5-HT to the injection, so that intrahypothalamic injections of these agents may be made into the same region from which local blood flow is recorded.

The anterior hypothalamus was studied because NE and 5-HT are normally present in relatively high concentrations in this area (15, 16) and because it is a relatively large area of subcortical gray matter in the rabbit, with monoeponential \(^{133}\)Xe clearances suggesting homogeneity of blood flow. There is evidence, also, that local injections of NE and 5-HT into the hypothalamus cause changes in body temperature, and one way in which they could do so is by altering hypothalamic blood flow.

This paper therefore records the results of experiments designed to determine the effect of NE and 5-HT administered by intraventricular or intrahypothalamic injection on local cerebral blood flow in the hypothalamus of the conscious rabbit.

**Methods**

**GENERAL**

At least two weeks before the experiment, a headplate was fixed to the skull, under pentobarbital anesthesia, 30 mg/kg. This headplate, similar to that described by Cooper et al. (17), was placed so that the stereotaxic coordinates developed by Monnier and Gangloff (18) could be used to achieve access to the hypothalamus with thermistors or injection cannula. Subsequently, the animal was allowed at least two 3-hour sessions in the stocks for the purpose of acquainting it to the mild restraint required.

Experiments were performed in a room with the ambient temperature kept between 21 and 24°C and a variability during any single experiment of less than 1°C. The rabbits were restrained in conventional stocks, and their heads stabilized by a rubber-lined constraining apparatus. The procedure did not appear to cause any distress to the animals; at least 1 hour was allowed to elapse before any blood flow measurements were made.

Rectal temperatures were recorded with a glass bead thermistor mounted in a polyethylene catheter inserted at least 5 cm into the rectum. Hypothalamic temperature was measured with a small glass bead thermistor mounted in a nonbeveled needle (o.d. 0.5 mm) and placed with its tip in the anterior hypothalamus on the control side. The rectal and hypothalamic thermistors were connected to bridge circuits, the outputs from which were recorded on an ultraviolet (UV) recorder (SE 2005) and a digital data logging system (Solartron LY.1470).

In most experiments, arterial pressure was monitored via a 00 nylon catheter in the central ear artery, connected to an Ether blood pressure transducer, and in some, arterial \(P_{CO_2}\) was measured at intervals using a Radiometer electrode.

Fine injection cannulae, 0.4 mm o.d., were placed with their tips in the anterior hypothalamus in equivalent positions on either side of the midline; each cannula was connected via a 2-m length of 00 nylon tubing to a Hamilton 250-\(\mu\)l microliter syringe and the whole system filled with \(^{133}\)Xe-saline solution (5 me/ml) (Radiochemical Centre, Amersham, Bucks, England). The tips of the injection cannulae were 1.5 mm from the midline, and 3.0 mm from each other.

Microinjections of 5 to 10 \(\mu\)l \(^{133}\)Xe dissolved in sterile pyrogen-free normal saline (5 me/ml) were made into each side of the hypothalamus alternately. The duration of each injection was about 2 to 3 seconds. In most cases, at least 10 minutes was allowed between injections. The clearance rates of the \(^{133}\)Xe were monitored by an external collimated scintillation counter, amplifier, pulse height analyzer and ratemeter system, and recorded on the UV recorder and the digital data logger. The time constant of the ratemeter was either 3 seconds for the first 30 seconds of the clearance curve and 10 seconds thereafter, or was 10 seconds throughout. Since the half-decay time for \(^{133}\)Xe clearance from the site of injection was rarely less than 1 minute, and was usually about 100 seconds, \(T = 0.1 \, K\), where \(T\) is the time constant value RC of the ratemeter assembly, and \(K\) is the time constant value for the exponential decay of activity during clearance (the input
function). When this relationship holds, the observed rate of clearance, where \( T = 10 \) seconds, is very close to the input function rate of clearance.

Mean background activity, which was high (100 to 300 counts/sec) because of the two \(^{133}\)Xe-filled cannulas, was subtracted from the exponential clearance curve which followed each injection, and the half-decay time (\( t_d \)) was computed from the first 1 to 2 minutes of the semilogarithmic plot of the clearance curve. Figure 1 shows a typical clearance curve. The clearance of injected \(^{133}\)Xe was monoexponential in all experiments, suggesting homogeneity of flow within the area of diffusion of the tracer.

Blood flow (ml/100 g tissue/min) was calculated as

\[
F = \frac{100 \cdot \log_2 \cdot \lambda_{xe}}{t_d}
\]

where \( \lambda_{xe} \) is the brain-blood partition coefficient for \(^{133}\)Xe in the rabbit hypothalamus, and \( t_d \) is the half-decay time (min) of the clearance curve.

**PRELIMINARY EXPERIMENTS**

**Determination of \( \lambda_{xe} \)**

In a preliminary series of experiments we measured \( \lambda_{xe} \) in the rabbit hypothalamus. \( \lambda_{xe} \) is difficult to measure directly because \(^{133}\)Xe comes out of solution very rapidly when exposed to air. A double isotope method for the measurement of \( \lambda_{xe} \) was devised, the principle of which is as follows. \(^{133}\)Xe and \(^{125}\)I are both \( \gamma \)-emitters. Approximately equal doses of \(^{133}\)Xe and \(^{125}\)I-antipyrine (\(^{125}\)IAP) dissolved in saline were mixed and injected into the tissue studied. The simultaneous clearance of these two tracers was then measured with an external scintillation counter. In these circumstances, since the two isotopes are being cleared by the same blood flow, the ratio of their half-decay times will be related to the ratio of their respective \( \lambda \) values, thus

\[
\frac{t_d^{133}Xe}{t_d^{125}\text{IAP}} = \frac{\lambda_{xe}}{\lambda_{IAP}}
\]

The second series of experiments was designed to determine \( \lambda_{IAP} \). The nonvolatile \(^{125}\)I-antipyrine was dissolved in saline and injected intravenously into the animal. After equilibration was reached the animal was killed and \(^{125}\)I-antipyrine activity in the tissue and in blood was measured. Tissue and blood activities were corrected for the presence of free iodide, and the ratio of the \(^{125}\)I-antipyrine activity in unit mass of tissue and blood (\( \lambda_{IAP} \)) was calculated.

With \( t_d^{133}Xe, t_d^{125}\text{IAP}, \) and \( \lambda_{IAP} \) known, \( \lambda_{xe} \) could then be calculated. Preliminary experiments, based on this principle, details of which have been described elsewhere (19), produced a value for \( \lambda_{xe}/\lambda_{IAP} \) of 0.73 ± 0.08 (se) and \( \lambda_{IAP} = 1.02 ± 0.01 \) (se). \( \lambda_{xe} \) is therefore 0.74.

**Maintenance of Autoregulation**

Cerebrovascular autoregulation is easily abolished, for example, by trauma, vascular perfusion procedures, periods of circulatory arrest, arterial and local tissue hypoxia, hypercapnia, and deep anesthesia. Preliminary experiments were carried out to determine whether the trauma induced by the presence of the cannula and the microinjector...
The first experiments (two rabbits) were designed to test the assumption that there is no systematic difference in hypothalamic blood flow on either side of the midline. When this was demonstrated (see Results), the next series of experiments was planned as follows. In each experiment one side of the hypothalamus was designated the control side and received injections of $^{133}$Xe in saline only. The injection system on the opposite side was primed with the same solution, to which the drug under examination was added to make up the appropriate final concentration. 1-NE (as bitartrate) was used in doses of 1 $\mu$g/injection (11 injections in three experiments), 5 $\mu$g (18 injections in four experiments), 10 $\mu$g (5 injections in two experiments), 20 $\mu$g (5 injections in six experiments), 40 $\mu$g (18 injections in six experiments) and 200 $\mu$g (10 injections in two experiments).

In addition, in two experiments the effect of adding phenoxybenzamine, up to a final concentration of 50 $\mu$g/injection, to the 40 $\mu$g/injections NE-$^{133}$Xe-saline solution, was determined; and in a further three experiments the effect of 50 $\mu$g/injection phenoxybenzamine alone was recorded.

The doses of 5-HT creatinine sulfate were 5 $\mu$g (as 5-HT) (18 injections in four experiments), 20 $\mu$g (14 injections in four experiments), 40 $\mu$g (18 injections in five experiments) and 80 $\mu$g (13 injections in four experiments).

In all experiments, clearances of $^{133}$Xe were measured alternately on the control side and the test side, and the flow on the test side was expressed as a percent of the mean of the control flows immediately preceding and following it. Three, four, or five injections were made into each side of the midline during the course of any one experiment. Since in most cases at least 10 minutes was allowed to elapse between any two successive injections, the interval between successive injections on the same side was usually about 20 minutes.

The recording thermistor was positioned on the control side; its tip was 3 mm posterior to the tip of the control injection cannula.

### Intraventricular Injections

In this series, 22 experiments were performed, 13 involving norepinephrine and 9 5-HT. The rabbits were prepared in the manner described in the previous section. In these experiments, however, the hypothalamic blood flow was measured on one side only, and hypothalamic temperature measured on the same side. Another injection cannula was inserted with its tip in the

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**Table 1: Autoregulation of Hypothalamic Blood Flow**

<table>
<thead>
<tr>
<th>Mean arterial blood pressure range (mm Hg)</th>
<th>1-20</th>
<th>21-40</th>
<th>41-60</th>
<th>81-100</th>
<th>101-120</th>
<th>121-140</th>
<th>141-160</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. observations</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>14</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>BF (ml/100 g/min)</td>
<td>20.8</td>
<td>20.8</td>
<td>28.5</td>
<td>37.4</td>
<td>27.9</td>
<td>30.7</td>
<td>23.0</td>
</tr>
<tr>
<td>SE</td>
<td>3.8</td>
<td>0.6</td>
<td>0.1</td>
<td>4.1</td>
<td>3.0</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Mean F/MF (ratio of BF to the mean BF at a mean arterial blood pressure of 81-100 mm Hg)</td>
<td>0.55</td>
<td>0.75</td>
<td>1.07</td>
<td>1.02</td>
<td>1.00</td>
<td>1.09</td>
<td>1.10</td>
</tr>
<tr>
<td>SE</td>
<td>0.17</td>
<td>0.14</td>
<td>0.43</td>
<td>0.055</td>
<td>0.086</td>
<td>0.14</td>
<td>1.16</td>
</tr>
<tr>
<td>t</td>
<td>2.64</td>
<td>1.57</td>
<td>0.16</td>
<td>0.20</td>
<td>1.36</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

BF = hypothalamic blood flow in ml/100 g/min; F/MF = ratio of BF to the mean BF at a mean arterial blood pressure of 81-100 mm Hg, which was taken as the "normal" range, and the mean hypothalamic blood flow for each rabbit at that pressure called 1. All other flows in that experiment at other blood pressure levels were expressed as a ratio of this value. This allowed a comparison between different animals, which vary considerably in their "normotensive" hypothalamic blood flow values.

$P$ = significance of difference from control mean F/FM ratio of 1.
froh= blood flow (ml/100 g/min) in the hypothalamus to the right (R, dotted line) and left (L, solid line) of the midline. Each circle represents one injection of tracer. 133Xe only injected on both sides. T_h = hypothalamic temperature.

opposite lateral ventricle, for the injection of NE, 5-HT, or a saline control. Rectal and hypothalamic temperature and hypothalamic blood flow were recorded as before.

The preliminary intraventricular injection of 0.2 ml of normal saline alone resulted in a variable, small (<0.1°C), and transient (<1 minute) fall of hypothalamic temperature and had no effect on hypothalamic blood flow, rectal temperature, or arterial blood pressure.

In each experiment at least two basal measurements of hypothalamic blood flow were made, followed by injection into the lateral ventricle of 20 |g norepinephrine dissolved in 20 |l sterile pyrogen-free normal saline or 200 |g 5-HT in 0.2 ml saline. Hypothalamic blood flow measurements were then made at 20-minute intervals for at least 1 hour. Each measurement was expressed as a percent of the mean of the basal flow readings.

As a control series for the experiments involving the intraventricular injections of NE and 5-HT described above, eight experiments were performed (49 blood flow readings) in which the conditions of these NE and 5-HT experiments were reproduced exactly, except that a saline (0.2 ml) control was used instead of the NE or 5-HT solution. This provided an indication of changes in hypothalamic blood flow with time.

Results

Intrahypothalamic Injections

Equality of Flow on Both Sides of the Midline.—Figure 2 shows the results of one experiment. There was no systematic difference in blood flow on the two sides in this experiment. In these experiments, microinjections of 133Xe were given on alternate sides, and blood flow on the right side calculated as a percent of the mean of the preceding and succeeding flows on the left side.

In eight comparisons of this kind, blood flow on the right averaged 101 ± 1.4% (se) of that on the left. This value is not significantly different from 100% (t = 0.71, P > 0.2), so that the use of flows on one side as a control for flow changes on the opposite (test) side appeared to be valid.
LOCAL NE, 5-HT AND HYPOTHALAMIC BLOOD FLOW

Effect of intrahypothalamic injection of NE on hypothalamic blood flow (F_j). Each point represents one injection on the NE-treated side. Abscissa: Dose of NE in µg/injection. The mean and SE for each dose is shown. n = number of blood flow values (NE-treated side) in each group; x = mean; ± = SE; P = significance level for the difference of each mean from 100%.

Intrahypothalamic Norepinephrine.—Figure 3 shows, in one experiment, that 1 µg NE/injection increases hypothalamic blood flow; this is true of all the results using norepinephrine in this dose, the mean being 155.0 ± 12.7% (SE), of flow on the control side (P < 0.0025, n = 11).

The results for 2 µg NE/injection showed a large scatter (Fig. 4), with a very slight but not significant decrease in blood flow, the mean being 96.4 ± 23.9% (SE) of flow on the control side (P > 0.05, n = 18). The three highest points were values from one experiment; in the other three, most or all of the values indicated a vasoconstrictor effect.

The results of experiments in which larger NE doses were used (10, 20, 40, 200 µg/injection) are shown in Figures 4 and 5. At all of these dose levels hypothalamic blood flow on the treated side was less than on the control side. At all dose levels, NE produced a small rise in the core temperature, but no significant change in systemic arterial pressure in those experiments in which it was recorded. The range of arterial Pco2 values was 33.8 to 41.2 mm Hg; there was no consistent or significant change in arterial Pco2 induced by the NE injections.

Phenoxybenzamine.—Addition of 50 µg of phenoxybenzamine to the 40-µg injections of NE abolished the vasoconstrictor action of NE. In fact, the blood flow increased by 37.4% ± 10.9% (t = 3.6, P < 0.0025) (Fig. 6). Phenoxybenzamine alone (50 µg/injection)
Effect of phenoxybenzamine (PBZ) on the vasoconstriction produced by 40 fig NE. Each point represents one injection. The test solutions, all dissolved in the 18Xe-saline solution on the test side, were 50 fig PBZ (3 experiments), 40 fig NE (6 experiments) and 50 fig PBZ and 40 ng NE together (2 experiments). The points for the 40 fig NE alone are the same as those shown in Figure 4.

increased hypothalamic blood flow by a mean of 52.6% ± 13.6% (t = 3.9, P < 0.0025).

Intrahypothalamic 5-HT.—When the higher doses (20 to 80 fig/injection) of 5-HT were injected, the hypothalamic blood flow was significantly greater on the 5-HT side than on the control side. The blood flow values were 124% (20 µg/injection), 154% (40 µg) and 169% (80 µg) of flow on the control side. The mean hypothalamic blood flow value on the 5-HT side following injection of a lower dose (5 µg/injection) did not differ significantly from 100%. The means, standard errors, and levels of significance are shown in Figure 7. At all dose levels 5-HT produced a small (0.05° to 0.2°C) transient (<10 minutes) fall in hypothalamic and rectal temperatures in all cases. No changes in arterial pressure or Pco2 were recorded following the 5-HT injections.

INTRAVENTRICULAR INJECTIONS

Control Experiments.—In eight experiments, two consecutive measurements of hypothalamic flow were made and their average used as the basal flow. Then, after a control injection of saline, repeated measurements of flow were made over the succeeding 2 hours. The results are shown in Figure 8. There was a fair amount of variability, and the mean blood flow values rose slowly with time, though the mean levels did not deviate significantly from the basal flow until 90 minutes had elapsed. This slow rise in clearance may be due to inflammatory changes around the cannulas.

Intraventricular NE.—Blood flow measurements for each 20-minute period after intraventricular NE (20 µg) were averaged and
LOCAL NE, 5-HT AND HYPOTHALAMIC BLOOD FLOW

FIGURE 9

Effect of intraventricular 5-HT and NE on hypothalamic blood flow. Ordinate: hypothalamic blood flow as percent of the preinjection (basal) flow. Abscissa: time after injection of 200 μg 5-HT (left figure) or 20 μg NE (right figure) into the lateral cerebral ventricle. Results are grouped in 20-minute periods, and the mean and SE for each period are shown.

compared with basal flow. Figure 9 shows the results for NE given in this way. It is clear that the results, although quite variable, show a trend to an increase in blood flow, which is significant at 20 to 40 minutes (123.6 ± 8.0%) (SE), (P < 0.05, n = 12). The mean of the values for over 40 minutes is 109.8%, which would suggest that the blood flow, although still raised (P < 0.05), was returning to control values. Similar levels of significance were obtained when these results were compared with the mean flows seen after saline injection in the control series shown in Figure 8. No change in arterial blood pressure was produced by NE in any of these experiments. In one, there was no change in hypothalamic temperature; in the others, it rose 0.1 to 0.8°C.

Intraventricular 5-HT.—The results of these experiments are shown in Figure 9; mean values for each 20-minute period were compared to 100% and also to mean values for the same expression derived from the control experiments (Fig. 8). The scatter of blood flow values was large. There was a fall in mean flow to 76.1 and 77.6% of the mean control value in the periods 0 to 20 and 20 to 40 minutes, respectively, but in neither period was the fall statistically significant.

In this series of experiments the fall in hypothalamic and rectal temperatures was of the same order (0.05° to 0.2°C) but lasted longer (up to 30 minutes) than that produced by 5-HT injected directly into the hypothalamus. No 5-HT-induced change in arterial blood pressure was seen nor was there any significant change in arterial Pco2.

Discussion

METHOD

The clearance of the injected 133Xe appeared to be monoeponential, at least down to 5 to 10% of the count rate above background. At this level, when the activity approached the high background level, the scatter of points on a semilogarithmic plot of the clearance was so great that it was not possible to continue the regression line down to background. It is therefore impossible to exclude with absolute certainty a second component to the curve; if such a component exists, it must be very small.

The finding that the 133Xe clearance curves (both in the control studies and after the local injection of NE and 5-HT) were monoeponential has several implications. The first is that flow was homogeneous within the area of diffusion of the tracer; the second is that if there was leakage of xenon along the cannula...
tract (even though the cannula was left in situ throughout the experiment) the tracer remained within a homogeneously perfused region. If, after the NE or 5-HT injections, the flow was continuously changing during the period of measurement, the clearance of the indicator might be expected to deviate from a monoexponential function. Another conclusion, therefore, from the monoexponential clearances of the tracer after the drug injections, is that new steady-state conditions are achieved rapidly compared to the rate of clearance of the indicator, and are maintained for at least as long as the linear portion of the clearance curve.

The maintenance of autoregulation, which in other circumstances is readily abolished by trauma and ischemia, is another factor in support of the validity of this technique. It is not suggested that local blood flow is not affected by the presence of the injection cannula, but the use of an identical injection system on the control side permits at least semiquantitative observations on the effects of vasoactive drugs on local flow.

NOREPINEPHRINE

Haggendal (1) has demonstrated a vasoconstricting effect on cerebral vessels, of intravenously infused norepinephrine in the dog. In normotensive man, pressor doses of L-norepinephrine, whether administered intramuscularly (20) or by continuous intravenous infusion (2-4) produced either no change or a small fall in cerebral blood flow. The resulting increase in cerebrovascular resistance was interpreted at that time as indicating a cerebral vasoconstrictor action of NE (20). However, since the existence of cerebrovascular autoregulation is now recognized, it is clear that an increased resistance can also occur in response to an elevated systemic arterial blood pressure. Thus the increase in cerebrovascular resistance following NE injection or intravenous infusion does not necessarily imply that the drug has a direct effect on the cerebral vasculature.

Green and Denison (21), using an electromagnetic flowmeter to measure blood flow continuously in an isolated canine cerebral circulation preparation, showed that intracarotid injections of NE had no effect on the cerebral vascular bed. Greenfield and Tindall (22) investigated this problem in man. Arterial blood pressure and flows in the internal and external carotid artery were measured continuously with electromagnetic flowmeters during surgical exposure of these vessels. Intravenous administration of NE was accompanied by an increase in cerebrovascular resistance, injections of NE into the external carotid artery were accompanied by an immediate decrease in blood flow through that artery due to a direct action on the vascular bed supplied by the external carotid, but NE injections into the internal carotid artery had no immediate effect. They concluded that NE had no direct action on the cerebral vascular bed but that the increased cerebral vascular resistance following intravenous administration of NE was due to autoregulation.

The results of the present study suggest that there is a dose-dependent opposite effect of NE on hypothalamic blood flow in the conscious rabbit when the amine is injected directly into the hypothalamus. Doses of 1 mg/injection increase local flow, and doses of 10 mg or more/injection reduce the hypothalamic blood flow, compared to the opposite (control) side. These alterations in flow were not due to changes of arterial pressure or PaCO2.

The vasoconstrictor effect of 40 μg/injection of NE into the hypothalamus was prevented by the addition of 50 μg of the alpha-receptor-blocking drug phenoxybenzamine. This would suggest that NE activates alpha receptors in hypothalamic vessels. It remains an open question whether the effects of the relatively large doses used in this study provide any indication of a physiological role of the amine. Also, it is obviously impossible to predict the response of vessels in other areas of the brain; it is quite possible that there is a regional variability in the responsiveness of cerebral vessels to exogenous NE.

On intraventricular injection of NE, there was a variable rise of hypothalamic blood
LOCAL NE, 5-HT AND HYPOTHALAMIC BLOOD FLOW

flow, maximal at 20 to 40 minutes after injection, and subsiding thereafter. One possible explanation for this effect is that NE diffuses from the ventricular system into the hypothalamus to produce a hypothalamic concentration, at least in the 20 to 40 minute period after intraventricular injection of 20 μg NE, equivalent to that produced by repeated local injections of a vasodilating dose, namely 1 μg NE/injection. In the 40 to 60 minute period, clearance or inactivation of NE in the hypothalamus might have reduced the effective local concentration, and the blood flow tended to return to control values.

Injection of NE into the cerebral ventricle or hypothalamus of the rabbit causes an increase in body temperature (17). It is possible that hypothalamic NE and 5-HT are concerned, as neurotransmitters, in the regulation of body temperature, but it has been suggested that the injection of these agents causes local alterations in hypothalamic temperature by influencing blood flow. This seems extremely unlikely, because intrahypothalamic NE causes a rise of body temperature at all doses, and the effects on flow are different at high and low doses.

5-HYDROXYTRYPTAMINE

The reported effect of 5-HT on systemic blood pressure and organ blood flow varies greatly according to the animal species, the anesthetic used, the route of administration, and the dose. For example, 5-HT causes vasoconstriction of most mammalian vessels—human forearm and umbilical vessels, rabbit ear artery and pulmonary vessels—and this is abolished by lysergic acid derivatives (23-26).

The present study has shown that 5-HT, when injected into the rabbit hypothalamus in doses of 20, 40 and 80 μg, causes a local vasodilatation. This is unlikely to be due to a nonspecific effect of body temperature change on hypothalamic blood flow, since an increase in flow may be produced by an increase in skin and core temperature by radiant heating (unpublished data). In the case of 5-HT, however, the increment of hypothalamic flow was associated with a small transient and variable fall in core temperature and cannot therefore be caused by it. On the other hand, one intraventricular injection of 200 μg of 5-HT is followed by a sustained fall in hypothalamic flow. The mechanism of this effect can only be speculated upon. It is reasonable to suppose that this action of 5-HT is a local vasomotor effect in the brain and not the result of any change in systemic arterial pressure or PCO₂, since no such change was observed in the rabbits in which these variables were measured. Also there is no reason to believe that autoregulatory capacity was impaired in the 5-HT experiments although this was not tested directly.

A dose-dependent, opposite effect has been described with reference to the intravenous 5-HT action on arterial blood pressure (27) and appears to apply to NE in the rabbit hypothalamus, so it is not inconceivable that a similar relationship exists for 5-HT. This is unlikely but cannot be entirely excluded on the available evidence. Unlike the NE injections, in which the smallest dose had an effect opposite to that of the larger doses, local injections of 5-HT showed no dose-dependent opposite effect in these experiments. It may be that doses of 5-HT even smaller than 5 μg/injection are vasoconstrictor. This would seem unlikely as the local dose of NE which was vasodilator (1 μg/injection) was one-twentieth of the vasodilator 20 μg intraventricular dose, whereas the smallest dose of 5-HT tested (5μg/injection), which had no significant effect on local flow, was one-fourth of the vasoconstrictor 200-μg intraventricular dose.

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Circ Res. 1971;28:492-502
doi: 10.1161/01.RES.28.4.492

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