Response of Local Blood Flow in the Caudate Nucleus of the Cat to Intraventricular Administration of Histamine

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SUMMARY The effect of intraventricular histamine on blood flow in the caudate nucleus of the cat was studied by means of the hydrogen clearance technique. Bilateral ventriculo-cisternal perfusion was installed. After a control period during which both lateral ventricles were perfused with mock CSF with the same composition, the drug under study was added to one side (experimental side) while the other side was perfused further with the control mock CSF (control side).

At each point in time, blood flow at the experimental side was compared to that at the control side. Histamine (10⁻³ M) caused a severe vasodilatation and this effect was completely antagonised by the H₂-receptor blocker cimetidine (10⁻² M). Cimetidine had no vasoactive effects of itself in the concentration used. The H₂-receptor agonist Dimaprit (10⁻³ M) had a vasodilator effect although less important than histamine.

Indirect evidence was gained that H₂-receptors are not active in the vascular bed under study.

Stroke Vol 13, No 4, 1982

HISTAMINE is a potent vasoactive substance that is present in most tissues in variable concentrations. Direct local application of the substance on superficial brain arteries has shown dilatory effects in cats¹⁻⁶ although no effect was reported in mice.⁷ Pial arteries in the cat thus appear to dilate in a dose dependent manner upon perivascular application of histamine and this vasodilatation is mediated by H₂-receptors.¹⁻⁵

In the present experiments the effect of histamine on the local blood flow in the deeper parenchyma of the cat brain was investigated.

Materials and Methods

Experiments were carried out on anesthetized (pentobarbital 30 mg/kg), paralysed (gallamine 10 mg/kg) and artificially ventilated cats (30% O₂, 70% N₂) weighing approximately 3 kg. Appropriate anesthesia and relaxation was maintained by additional doses of pentobarbital (5 mg/kg) and gallamine (3 mg/kg) every hour. The animals were placed in a stereotaxic apparatus and a bilateral ventriculocisternal perfusion (VCP) was installed in a similar way as described in a previous communication of our laboratory.⁸ Two inlet-cannulae, one on each side, were lowered in the lateral cerebral ventricles with a microdrive system. Through these cannulae, artificial cerebrospinal fluid was administered at a rate of 0.123 ml/min (Harvard Infusion-withdrawal pump model 901). An outlet cannula was placed in the suboccipital cistern. The perfusion pressure was continuously monitored at both sides. The composition of the mock CSF was as follows (mmol/l): NaCl 138; KCl 3.3; NaHCO₃ 25.0; NaH₂PO₄·H₂O 0.5; MgCl₂·6H₂O 1.2; CaCl₂ 1.25; glucose·H₂O 3.1.

Substances under study were added to the mock CSF. Osmolality and bicarbonate concentration were carefully checked and if necessary adjusted to 320 mOsm/kg and 25 mmol/l respectively. Blood gases were controlled and the animals were kept in steady state normocapnia (paco₂ 30-40 mm Hg) by adjustment of ventilation. Blood pressure was monitored during the entire experiment; in the experiments reported mean blood pressure was at least 100 mm Hg.

CBF measurement

Blood flow was measured simultaneously in both caudate nuclei with the hydrogen clearance method.⁹,¹⁰ Two hydrogen sensitive electrodes (glass insulated platinized platinum iridium wire Ø 0.35 mm) — one on each side — were stereotaxically placed in the head of each caudate nucleus (coordinates A₁₇; L₄; H₂) according to the stereotaxic atlas of Snider and Niemer.¹¹ The animals were saturated with hydrogen, by adding 10% hydrogen gas to the inspired air. Hydrogen ad-
ministration was discontinued after a saturation period of at least 10 minutes to allow the arterial hydrogen concentration to fall to zero. Calculation of CBF from the desaturation curves started 40 s after cessation of the hydrogen administration. Hydrogen concentration was recorded continuously and in addition the instantaneous hydrogen concentration was measured with intervals of 10 s by a teletype interface and the data put on punched tape for computerised analysis. From the discontinuous data the desaturation curve was reconstructed and plotted semilogarithmically versus time by a Hewlett-Packard 9810 A calculator and a HP 9862 A plotter. In most cases this procedure yielded a biexponential decay and the regression lines of the fast and slow component were calculated by the least square method; herefrom the flow value was calculated, assuming a partition coefficient of 1.9

Mean flow was calculated according to the formula:

\[ F_m = F_f \times W_f + F_s \times W_s \]

where \( F_m \), \( F_f \), and \( F_s \) stand for mean flow and flow of the fast and slow compartment respectively, \( W_f \) and \( W_s \) stand for the relative weight of the fast and slow compartment. The relative weights of both compartments were assumed to be proportional to their hydrogen concentration at saturation; these were calculated by extrapolation of the linear regression lines of both compartments to the point in time where their sum equaled the "mean" hydrogen concentration measured by the electrode when brain tissue was saturated. From the mean flow values in both caudate nuclei, which were simultaneously measured, the blood flow ratio \( E/C \) (flow experimental side/flow control side, see further) was calculated.

Experimental Design
Each experiment was started with a symmetrical perfusion with mock CSF (normal or with additives) and the first flow measurement was made one hour after the start of the VCP. During this control period three control flow measurements were made with a 45 min interval.

After the third control measurement, the composition of the perfusion fluid was changed at one side (experimental side: E) while at the other side (control side: C) perfusion was continued with the same solution as during the control period (t = 0). Thereafter three flow measurements were made again with a 45 min interval.

Four series of experiments were performed. In a first series (n = 7) histamine \( 10^{-3} \) M was added to the experimental side after a control period on "pure" mock CSF. If in the control period caudate nucleus blood flow was not symmetrical, histamine was added to the side which showed the lower blood flow (see discussion).

In a second series (n = 5) both sides were initially perfused with mock CSF containing histamine \( 10^{-3} \) M; thereafter the \( H_2 \)-receptor blocker cimetidine \( (10^{-2} \) M) was added to the experimental side. If in the control period blood flow was not symmetrical, cimetidine was added to the side which showed the higher blood flow.

In a third series (n = 5) the \( H_2 \)-receptor agonist dimaprit \( (10^{-3} \) M) was added to the experimental side after a bilateral control perfusion with pure mock CSF. As in the histamine series, dimaprit was added to the side which in the control period showed the lower blood flow.

In a fourth series (n = 6) both lateral ventricles were initially perfused with mock CSF containing cimetidine \( (10^{-2} \) M). Thereafter histamine \( (10^{-3} \) M) was added to one side.

Statistical analysis of the results was performed using the Student t-test for paired observations.

Results
The blood flow values obtained in the caudate nuclei of the control and experimental sides are represented in the table (mean values ± SEM).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>1st series</th>
<th>2nd series</th>
<th>3rd series</th>
<th>4th series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Experimental side</td>
<td>Control</td>
<td>Experimental side</td>
</tr>
<tr>
<td>0-90</td>
<td>69 ± 19</td>
<td>54 ± 10</td>
<td>92 ± 16</td>
<td>115 ± 25</td>
</tr>
<tr>
<td>0-45</td>
<td>65 ± 16</td>
<td>52 ± 8</td>
<td>104 ± 23</td>
<td>115 ± 25</td>
</tr>
<tr>
<td>0</td>
<td>74 ± 16</td>
<td>56 ± 9</td>
<td>108 ± 22</td>
<td>120 ± 28</td>
</tr>
<tr>
<td>45</td>
<td>68 ± 12</td>
<td>103 ± 21</td>
<td>105 ± 23</td>
<td>89 ± 22</td>
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<tr>
<td>90</td>
<td>64 ± 10</td>
<td>115 ± 19</td>
<td>113 ± 23</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>135</td>
<td>60 ± 12</td>
<td>118 ± 18</td>
<td>113 ± 22</td>
<td>63 ± 14</td>
</tr>
</tbody>
</table>

First series: ventriculo-cisternal perfusion with mock CSF: At time = 0 histamine \( (10^{-3} \)M) was added to the perfusate on the experimental side;
Second series: ventriculo-cisternal perfusion with mock CSF to which histamine \( (10^{-3} \)M) was added. At time = 0 cimetidine \( (10^{-2} \)M) was added to the perfusate on the experimental side;
Third series: ventriculo-cisternal perfusion with mock CSF. At time = 0 dimaprit \( (10^{-3} \)M) was added to the perfusate on the experimental side;
Fourth series: ventriculo-cisternal perfusion with mock CSF to which cimetidine \( (10^{-2} \)M) was added. At time = 0 histamine \( (10^{-3} \)M) was added to the perfusate on the experimental side.

Table: Blood Flow (ml/min/100 g) in the Caudate Nuclei of Anesthetized, Curarized and Artificially Ventilated Cats During Ventriculo-Cisternal Perfusion

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In the first series of experiments mean values of the blood flow in the caudate nuclei varied in the control period (t = −90 to t = 0) between 65 and 74 on the control side and between 52 and 56 ml/min/100 g on the experimental side. Addition of histamine at t = 0 to the ventricular perfusate of the experimental side almost doubled the blood flow. The “blood flow ratio E/C” which was 0.89 ± 0.08 at t = 0, increased to 2.26 ± 0.41 at t = 135 (p < 0.01) (fig. 1), indicating vasodilatation by histamine.

In the second series of experiments when both lateral ventricles were perfused with mock CSF containing cimetidine, blood flow in the caudate nuclei varied between 92 and 108 ml/min/100 g on the control side and between 115–120 ml/min/100 g on the experimental side. Addition of cimetidine at t = 0 to the ventricular perfusate decreased the blood flow of the experimental side by about 50%. “Blood flow ratio E/C” which was 1.25 ± 0.23 at t = 0 decreased to 0.61 ± 0.10 at t = 135 (p < 0.02) (fig. 2).

In the third series of experiments the mean values of the blood flow in the caudate nuclei at the end of the control period with perfusion of simple mock CSF were 67 and 96 ml/min/100 g respectively at the experimental and control sides. Addition of the H2-receptor agonist dimaprit slightly increased the blood flow at the experimental side while a decrease was seen at the control side. “Blood flow ratio E/C” was 0.70 ± 0.05 at t = 0 and increased to 1.34 ± 0.19 at t = 135 (p < 0.02) (fig. 3).

In the fourth series of experiments, when both lateral ventricles were perfused with mock CSF containing cimetidine, blood flow in the control period (t = −90 to 0) increased progressively from 54 to 66 on the control side and from 55 to 69 ml/min/100 g on the experimental side. After addition of histamine at t = 0 to the ventricular perfusate of the experimental side, blood flow remained practically constant. “Blood flow ratio E/C” was 1.08 ± 0.15 at t = 0 and 1.02 ± 0.12 at t = 135 (indicating no change (fig. 4).
terminals and in mast cells. The latter are often located around cerebral blood vessels which raises the possibility of a histaminergic effect on local blood flow through influence on the local cerebral vascular resistance. Such an effect of histamine was observed on superficial brain vessels. The present experiments show that this reactivity is not unique to pial vessels and that deeper vascular beds such as that of the caudate nucleus react in the same way as the superficial vessels.

Wahl and Kuschinsky applied histamine directly on the pial blood vessels and effects were seen at much lower concentrations ($10^{-8}$ to $10^{-4}$ M) than in our experiments ($10^{-3}$ M). In our experimental model lower concentrations ($5.10^{-4}$ and $10^{-5}$ M) of histamine gave inconstant results (a very small vasodilatation or no detectable change). The concentration of histamine in the ventricular CSF was undoubtedly lower than in the infused mock CSF because of addition of freshly secreted endogenous CSF. In addition histamine had to diffuse into the periventricular brain tissue before its effect on the blood flow in the caudate nucleus could be detected by the method employed. Due to diffusion time and possible metabolisation, the histamine con-

**Discussion**

The first series of experiments indicates that infusion of histamine $10^{-3}$ M in the lateral ventricle produces an important vasodilatation in the caudate nucleus of the cat. Infusion of mock CSF containing histamine into the lateral ventricle increased the "blood flow ratio E/C" from 0.89 to 2.26. It could be argued that, due the deliberate choice to add histamine to the side with the lower flow, our experiments only indicate vasodilatation by histamine provided there is an initial low flow state (ratio < 1). The fact, however, that the qualitative relationship between the flow on both sides inverses (the ratio becoming > 1) invalidates such argument. The same remark holds for the cimetidine and dimaprit series which also present an asymmetrical blood flow in the control period.

In general histamine is a potent vasoactive substance that is present in most tissues in variable concentrations. This substance, together with specific enzymes for its metabolism, is also present in the brain. Its distribution in different regions of the brain is very uneven and different histologic compartments have also been described such as a localization in nerve terminals and in mast cells. The latter are often located around cerebral blood vessels which raises the possibility of a histaminergic effect on local blood flow through influence on the local cerebral vascular resistance. Such an effect of histamine was observed on superficial brain vessels. The present experiments show that this reactivity is not unique to pial vessels and that deeper vascular beds such as that of the caudate nucleus react in the same way as the superficial vessels.

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**Figure 3.** as fig. 1. Dimaprit $10^{-3}$ M: mock CSF to which dimaprit was added. Addition of dimaprit causes vasodilatation.

**Figure 4.** as fig. 1. Administration of cimetidine prevents vasodilatation by histamine.
centration in the extracellular fluid of the caudate nucleus where the blood flow was measured, can be accepted to be much lower than that in the ventricular CSF. It was found that after 1 h of epiarachnoid irradiation the mean concentration of exogenous histamine in the first 1 mm of brain subjacent to the irradiating solution was approximately 15% of the concentration of histamine in the irrigation fluid. The histamine concentration decreased further by approximately one-half for each additional 0.4 mm that the tissue was located further from the surface.

In vascular beds, histamine can have different effects due to balanced interaction with H₁ and H₂-receptors. In most tissues activation of H₂-receptors causes vasodilatation and activation of H₁-receptors causes vascular reactions which vary according to species and regions in the vascular system. Different histamine receptor distribution and/or characteristics is made responsible for the different activities of histamine in various species or in different vascular beds of the same species.

The second series of experiments indicates that addition of the H₂-receptor blocker cimetidine reverses the vasodilatation caused by histamine. Infusion of mock CSF containing cimetidine into the lateral ventricle decreased the "blood flow ratio E/C" from 1.25 to 0.61. Separate experiments indicated that in the absence of exogenous histamine, cimetidine did not affect the blood flow in our experimental model. Therefore we can conclude that the vasodilatation by histamine in the cat brain takes place through interaction with H₂-receptors. Similar conclusions were gained on pial vessels. In addition, the lack of effect of cimetidine in the absence of exogenous histamine suggests that in our experimental conditions endogenous histamine was of minor importance for the tone of the brain vessels.

The third series of experiments indicates that the selective H₁-receptor agonist dimaprit also causes a vasodilatation in the brain tissue. Infusion of mock CSF containing dimaprit into the lateral ventricle increases the "blood flow ratio E/C" from 0.70 to 1.34. For an equimolar dose the effect of dimaprit appears to be less than that of histamine. Such smaller effect is not extraordinary, since most of the selective histamine receptor agonists have a weaker action than histamine itself (dimaprit has only about 70% of the positive chronotropic activity of histamine on the right atrium preparation of the guinea pig, an effect mediated by H₁-receptors).

Investigating H₂-receptor mechanisms on brain vessels is somewhat more difficult. A possible (weaker) vasodilating response of pial arteries to the H₂-receptor stimulating substance 2-(2-pyridyl) ethylamine was recently reported. Unfortunately, most of the H₂-receptor agonists (e.g. 2-(2-pyridyl) ethylamine) still have a considerable activity at H₁-receptor sites. On the other hand the H₁-receptor antagonists (e.g. mepyramine) produce an atypical vasodilatation due to a direct action on vascular smooth muscle. Such vasodilatation makes the interpretation of an effect of mepyramine difficult. We therefore investigated the possible role of H₁-receptors indirectly, examining the effect of histamine while the H₂-receptors were blocked. The results indicate that histamine in these conditions causes no vascular changes.

Intraventricular and intracerebral administration of histamine produces changes in behavior and electrical activity in selected brain areas. Due to the tight coupling between function, metabolism and flow in the brain the interpretation of the observed vasodilatation becomes difficult. Vasodilatation might either indicate a direct vascular effect of histamine or be secondary to an increased functional or metabolic state of the brain. Such dual contribution was already discussed by Harper and associates when studying the effect of noradrenaline, 5-hydroxytryptamine and dopamine on CBF. Separation of direct vascular effects from those mediated by metabolic or functional changes needs simultaneous measurement of electrical activity or metabolic rate. Such measurements were not performed in our study but another study indicates that topical application of histamine increases local cortical blood flow without affecting local electrical activity.

The local and direct application of histamine thus appears to cause regularly dilatation of the brain blood vessels and to increase cerebral blood flow. In this respect the results obtained in several brain regions are much more concordant than the effects observed in vivo with systemic intravascular (intravenous, intrarterial) administration of histamine where increases in cerebral blood flow as well as no changes have been reported. Such divergences may be due to differences in general cardiovascular reaction (blood pressure, cardiac output) as well as to the existence of a blood-brain barrier modulating or excluding to the large extent the effect of histamine on the brain vasculature.

Footnote

After this paper was submitted for publication two papers were published, dealing with the effect of histamine on cerebral blood flow and pial vasculature respectively. They indicate that the vasodilatation caused by histamine is not limited to pial vessels but extends to deeper structures. In addition it was found that intracarotid infusion of histamine after osmotic opening of the blood-brain barrier does not change the metabolic rate for glucose, suggesting that the increases in blood flow produced by histamine are the result of stimulation of vascular histamine receptors rather than a secondary response to metabolic activation.

References

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Response of local blood flow in the caudate nucleus of the cat to intraventricular administration of histamine.
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Stroke. 1982;13:499-504
doi: 10.1161/01.STR.13.4.499

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