Influence of Adrenergic Receptor Blockade on Circulatory and Metabolic Effects of Disordered Neurotransmitter Function in Stroke Patients

John Stirling Meyer, M.D., Yohsuke Miyakawa, M.D., K. M. A. Welch, M.D., Yoshifumi Itoh, M.D., Naoki Ishihara, M.D., Ewa Chabi, B.S.C., Janet Nell, Ph.D., Katherine Bartosh, M.S., and Arthur Dale Ericsson, M.D.

SUMMARY Cerebral hemispheric blood flow and metabolism were measured before and after therapy with intracarotid infusion of combined PBZ and PPL in 15 patients with recent cerebral infarction. HBF was unaltered despite decrease in cerebral perfusion pressure. Cerebral hemispheric oxygen consumption and carbon dioxide production decreased while cerebral hemispheric lactate production increased.

Biphasic cerebral uptake of tyrosine was observed during and immediately after PBZ and PPL infusion. CSF HVA increased, indicating altered DA turnover. CSF 5HIAA levels also increased, suggesting altered 5HT turnover after PBZ and PPL. Release of cyclic AMP from ischemic brain into cerebral venous blood seen in the steady state was abolished after therapy.

Introduction

INCREASING IMPORTANCE has been attributed to disordered neurotransmitter function in the pathogenesis of cerebral infarction. Studies in animals and clinical patients indicate that during cerebral ischemia there is excessive release of several putative neurotransmitters from damaged neurons, possibly at synaptic sites. Such release together with impairment of reuptake mechanisms and enzymatic catabolism may lead to extracellular accumulation of the neurotransmitter agent. The precise role played by extraneuronal neurotransmitter accumulation in the pathogenesis of cerebral infarction is not understood. Permanent depolarization of post-synaptic neuronal sites may occur as well as false neurotransmitter effects on neurons remote from the sites of neurotransmitter release. Such influences may account in part for disordered neurotransmission, intracellular edema and impaired cerebral metabolism. Diffusion of neurotransmitters away from the synaptic cleft with release into cerebral venous blood and CSF has been substantiated by previous studies.

An additional adverse effect of excessive neurotransmitter release may be the production of vasogenic edema and cerebral vasconstriction, thereby also causing impairment of collateral circulation and progression of ischemia to infarction.

On the assumption that disordered neurotransmitter function may be an important concern in the pathogenesis of cerebral infarction, therapeutic agents known to influence neurotransmitter function seem worthy of trial in an effort to correct the adverse symptomatology of this condition. In the present study, an attempt has been made to overcome the possibly adverse effects of presumed excessive pre-synaptic catecholamine release in ischemic brain of patients with recent thromboembolic cerebrovascular occlusive disease by blocking post-synaptic receptor sites using a combination of the respective alpha and beta receptor blockers, phenoxybenzamine (PBZ) and propranolol (PPL). The choice of this approach was decided by (1) previous demonstration of neuronal catecholamine release from ischemic brain in animals and man, (2) the correlation of such extraneuronal release with reduction of cerebral blood flow (CBF) and impairment of cerebral metabolism, (3) prior beneficial use of PBZ or PPL alone in a similar group of patients studied in this laboratory, and (4) studies from other laboratories which showed beneficial effects on experimental shock gained by the combined use of these two agents.

This paper reports the effect of combined use of PBZ and PPL on CBF, cerebral energy metabolism and central neurotransmitter function, and evaluates the therapeutic efficacy of central alpha and beta receptor blockade in patients with recent cerebral infarction.

Methods

CLINICAL CASE MATERIAL

Cerebral hemispheric blood flow (HBF) and metabolism were examined in 15 patients with acute or subacute cerebral ischemia and infarction confirmed by clinical examination, angiography, brain scan, EEG and CSF examination. Age, sex, clinical diagnosis, grade of severity of the neurological deficit and associated diseases considered to be risk factors as well as the interval of time between the ischemic episode and the time of study are listed in table 1.
Ten men and five women were studied, ranging in age from 43 to 75 years with a mean age of 56. The mean duration between onset of cerebral ischemia and the measurements was 13 days. Fourteen patients had cerebral hemispheric infarction and one had brainstem infarction. The clinical course and severity of the stroke were classified according to the following grading system into Grades 1 through 4:

Grade 1. Transient ischemic attack. The duration of localized neurological deficit did not exceed 24 hours and recovery was complete. No such cases were included in the present study.

Grade 2. Reversible ischemic neurological deficit. The neurological deficit, consisting of hemiparesis, monoparesis or dysphasia, persisted longer than 24 hours but recovery was virtually complete within three weeks. There were three patients studied with this grade of severity.

Grade 3. Presumed cerebral infarction with moderate residual disability. Moderate residual disability persisted after three weeks despite steadily progressive recovery. There were nine patients studied within this grade.

Grade 4. Presumed cerebral infarction with severe neurological deficit. A severe neurological deficit persisted after three weeks with little or no evidence of recovery thereafter. There were three patients included in the present study from this category.

PROCEDURE FOR OBTAINING INFORMED CONSENT

Suitable patients were selected for admission to the study by two or more staff neurologists after review of the patients' records and exclusion of cases where there was some medical contraindication to the procedure. Each patient was seen in consultation by a cardiologist and was not admitted to the study unless it was indicated in the record that there was no cardiological or general medical contraindication to the procedure. The procedure was described to the patient or the responsible relative on two separate occasions, first by a neurologist and then by a nurse who later witnessed the signing of a standard consent form. This consent form described how the catheters were to be placed, the possible risks involved and stated that further explanation or clarification would be provided upon request and that the patient might withdraw from the procedure at any time.

MEASUREMENT OF CEREBRAL CIRCULATION AND METABOLISM

Each patient was premedicated with meperidine hydrochloride, 50 mg i.m., and atropine sulfate, 0.4 mg i.m. Local anesthesia was induced at all puncture sites by infiltration with 1% procaine hydrochloride. A catheter was inserted under fluoroscopic control via the basilic vein into the ipsilateral cerebral transverse sinus for sampling of cerebral venous blood and measurement of intracarotid venous pressure (ICVP). A second catheter was placed into the superior vena cava to measure central venous pressure (CVP). A third catheter was inserted into the internal carotid artery ipsilateral to the side of the infarction in order to record arterial blood pressure (BP) and to inject a bolus of hydrogen-saturated saline and radioisotopes for CBF measurement. A final catheter was inserted into the brachial artery to sample arterial blood.

Lumbar puncture was performed and a catheter was placed in the subarachnoid space in a cephalad direction in order to monitor CSF pressure (CSFP) and to sample CSF. All pressures were continuously recorded with Statham pressure transducers.

Arterial and cerebral venous oxygen tension (Pao2), carbon dioxide tension (PCO2) and pH were recorded by means of electrodes mounted in flow-through cuvettes, and oxygen saturation (SO2) was monitored by means of reflection oximeters. An infrared absorption CO2 gas analyzer was used to measure arterial and cerebral venous total CO2 content.

PROCEDURE

The study was conducted according to the following protocol. After establishing steady state conditions, 10 mg of phenoxybenzamine (PBZ) combined with 2 mg of propranolol (PPL) diluted in 20 ml of normal saline were cautiously injected into the carotid artery ipsilateral to the infarcted hemisphere over an interval of 20 minutes. During the infusion, great attention was paid not only to the patient's clinical condition but also to blood pressure, pulse rate, ECG and EEG, which were continuously monitored. If

<table>
<thead>
<tr>
<th>Table 1 Case Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>
any of these parameters strongly indicated disadvantageous effects of the drugs, the infusion was interrupted or discontinued.

Measurement of HBF and metabolism were made in the steady state, immediately after infusion of combined PBZ and PPL and about 30 to 60 minutes post-infusion. For the measurement of HBF, a 10-ml bolus of hydrogen-saturated saline was injected into the carotid artery. The clearance curves of the hydrogen were recorded by a hydrogen electrode placed in the continuous flow cuvettes, and HBF was calculated from these curves by stochastic analysis.

Hemispheric metabolic indices for oxygen consumption (HMITOX), carbon dioxide production (HMICO2), glucose consumption (HMIGI) and hemispheric glucose to oxygen utilization ratio (HG:O) were calculated using formulas reported previously.

The cerebrovascular autoregulatory response to changes in cerebral perfusion pressure (CPP) was tested by tilting the patient’s head 30° (induced hypertension) before and after infusion of PBZ and PPL. The autoregulatory response was quantitated by using the autoregulation index (A.I.) calculated from the following formula:

\[ \text{A.I.} = \frac{\Delta \text{HBF}}{\Delta \text{CPP}}, \]

where \( \Delta \text{HBF} \) is the change of HBF that occurs with cerebral perfusion pressure change (\( \Delta \text{CPP} \)) as a result of induced hypertension or hypotension.

Cerebral arteriovenous differences for whole blood tyrosine (TYR) were continuously analyzed by drawing blood at a rate of 0.16 ml per minute into two Technicon Autoanalyzer systems via catheters placed in the brachial artery and cerebral transverse sinus. Cyclic AMP levels in plasma were analyzed in separate blood samples drawn from the same sites before and 60 minutes after PBZ and PPL infusion was discontinued. The separate blood samples obtained were also analyzed for glucose, pyruvate, lactate, inorganic phosphate (Pi), serum phospholipid phosphorus, triacylglycerols and angiotensin-I. CSF was sampled at the same intervals and analyzed for TYR, norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (5HT), homovanillic acid (HVA), 5-hydroxyindole acetic acid (5HIAA) and cyclic AMP.

**BIOCHEMICAL METHODOLOGY**

TYR in whole blood and CSF was measured by the use of the Technicon Autoanalyzer according to a modification of the method of Blau et al.11 DA, NE, and 5HT were measured in 3 cc of CSF which was first deproteinized using 0.4 M perchloric acid. DA and NE were isolated from the deproteinized specimen on activated alumina at pH 8.6. After prior organic extraction from the column effluent 5HT was assayed fluorometrically using a modification of the methods of Maickel and Miller12 and Curzon and Green.13 NE and DA were eluted from the alumina columns with acetic acid and the eluate halved. DA was analyzed fluorometrically in one portion according to a modification of the methods of Carlson and Waldeck14 and Anton and Sayre.15 The remaining portion was placed on Amberlite columns from which NE was eluted by 2/3 M boric acid and analyzed fluorometrically using the trihydroxyindole reaction according to modifications of the method of Renzini et al.16 and Valori et al.17 HVA and 5HIAA were organically extracted from CSF (usually 2.2 ml) using a modified combination of the methods of Ashcroft et al.18 and Gerbode and Bowers.19 Both compounds were fluorometrically assayed, 5HIAA by the technique of Ashcroft and Sharman20 and HVA according to Curzon et al.21 Cyclic AMP in CSF was analyzed by a protein binding assay similar to radioimmunoassay by a combination of the methods of Gilman22 and of Brown et al.23

Glucose was measured in arterial and cerebral venous blood by an enzymatic spectrophotometric technique.24 Lactate and pyruvate were measured by the enzymatic method of Rosenberg and Rush.25 Pi was measured by an automatic colorimetric method.26 Serum phospholipid phosphorus was measured by means of a semiautomated method using the Technicon Autoanalyzer.27 Total phosphatase was determined colorimetrically.28 Triacylglycerols and glycerol were determined using a semiautomated fluorometric method.29 Angiotensin-I was measured by radioimmunoassay.30

**Results**

**CEREBRAL HEMODYNAMIC EFFECTS OF COMBINED PBZ AND PPL**

Mean HBF values before and after infusion of PBZ and PPL are shown in table 2. HBF was unaltered either immediately after or one hour post-infusion despite a significant fall in MABP and increase in CSFP (figs. 1 and 2). Statistical analysis of values obtained from several subgroups differentiated on the basis of associated diseases such as diabetes mellitus, hypertension, severity of stroke and duration after onset of neurological deficit also showed no significant change of HBF after PPL and PBZ infusion.

In the steady state the mean A.I. for induced hypertension was 0.185, which indicates partial impairment of cerebral autoregulation. After combined PBZ and PPL the mean A.I. was reduced to 0.039, which would seem to indicate improved autoregulation due to improved vasodilator capacitance. However, this finding may be more apparent than real since there were paradoxical responses (negative A.I. values) recorded at this time (fig. 3) in some patients, which on calculation of mean values in the total group would approximate the A.I. closer to zero. The observed paradoxical responses to hypertension indicate excessive cerebral vasodilatation.

During induced hypertension the steady state mean A.I. was 0.200, again indicating partial impairment of cerebral autoregulatory vasoactivity. After PBZ and PPL infusion, A.I. became 0.108. Paradoxical responses were more frequently recorded at this time indicating an excessive cerebral vasoconstrictor response.

**SYSTEMIC METABOLIC EFFECTS OF COMBINED PBZ AND PPL**

Mean arterial levels of glucose, triacylglycerols, glycerol, total phosphate, Pi, phospholipids, pyruvate and lactate in the steady state and after the administration of PBZ and PPL are listed in table 3. The mean arterial glucose levels were abnormally high in the steady state due to the number...
TABLE 2  Effect of Combined PBZ and PPL Infusion on Hemispheric Blood Flow and Metabolism

<table>
<thead>
<tr>
<th></th>
<th>Steady state</th>
<th>Immediately after infusion (No. 1)</th>
<th>60 minutes after infusion (No. 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBF (ml/100 gm brain/min)</td>
<td>29.6 ± 2.6</td>
<td>29.6 ± 2.3 (N = 15)</td>
<td>29.9 ± 2.3 (N = 9)</td>
</tr>
<tr>
<td>HMIO₂ (ml/100 gm brain/min)</td>
<td>2.43 ± 0.53</td>
<td>2.43 ± 0.52* (N = 15)</td>
<td>2.43 ± 0.52* (N = 9)</td>
</tr>
<tr>
<td>HMICO₂ (ml/100 gm brain/min)</td>
<td>2.38 ± 0.52</td>
<td>2.38 ± 0.48* (N = 15)</td>
<td>2.11 ± 0.43 (N = 9)</td>
</tr>
<tr>
<td>HMIG₁ (mg/100 gm brain/min)</td>
<td>3.03 ± 0.92</td>
<td>3.03 ± 0.92 (N = 15)</td>
<td>3.35 ± 0.72 (N = 11)</td>
</tr>
<tr>
<td>HG:O</td>
<td>1.31 ± 0.35</td>
<td>1.31 ± 0.35 (N = 15)</td>
<td>1.50 ± 0.38 (N = 11)</td>
</tr>
<tr>
<td>HMI lactate (mg/100 gm brain/min)</td>
<td>0.139 ± 0.15 (N = 15)</td>
<td>0.139 ± 0.15 (N = 15)</td>
<td>0.267 ± 0.222* (N = 11)</td>
</tr>
<tr>
<td>HMI pyruvate (mg/100 gm brain/min)</td>
<td>0.030 ± 0.015 (N = 9)</td>
<td>0.030 ± 0.015 (N = 9)</td>
<td>0.055 ± 0.078 (N = 12)</td>
</tr>
<tr>
<td>HRQ</td>
<td>1.00 ± 0.10</td>
<td>0.97 ± 0.07 (N = 15)</td>
<td>1.00 ± 0.08 (N = 12)</td>
</tr>
</tbody>
</table>

*Significant as compared with steady state values.
N = number of cases.

Of diabetics in this series of cases. After combined PBZ and PPL infusion systemic levels of triacylglycerol, glycerol and total phosphate became significantly decreased while systemic glucose levels further increased. There was also a tendency for lactate levels to decrease in arterial blood.

Steady state mean angiotensin-I levels (expressed as ng/ml/hr of renin activity) in arterial blood was 3.27 ± 2.63 and decreased significantly to 1.76 ± 1.86 after PBZ and PPL (table 4).

CEREBRAL METABOLIC EFFECTS OF COMBINED PBZ AND PPL.

HMIA₂ and HMICO₂ decreased significantly immediately after PBZ and PPL infusion. However, the values 60 minutes after infusion no longer showed significant change from steady state (table 2, fig. 1). HMIGI and HG:O exhibited a tendency to increase, but did not reach the...
Effect of Combined PBZ and PPL Infusion on Arterial Concentration of Angiotensin-I (ng/ml/hr Expressed as Renin Activity)

<table>
<thead>
<tr>
<th>Group</th>
<th>A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state</td>
<td>3.27 ± 2.63</td>
</tr>
<tr>
<td>After infusion</td>
<td>1.76 ± 1.86*</td>
</tr>
</tbody>
</table>

*Significant as compared with steady state value.

Values = mean ± SD. N = number of cases.
In the latter group, although the mean of actual values showed only a strong tendency to increase, there was a significant mean percentage increase from steady state in the tyrosine uptake group (fig. 6). CSF NE levels were unchanged in either group (fig. 7).

In the total group studied, the significant cerebral A-V difference for cyclic AMP noted in the steady state was no longer apparent after PBZ and PPL infusion (table 6).

Discussion

Since intracarotid infusion of either alpha (PBZ) or beta (PPL) adrenergic blocking agents has been found in separate studies to produce some beneficial effects on CBF, cerebral autoregulation, metabolism, EEG and neurological deficit in patients with recent stroke, the present study was undertaken using PBZ and PPL combined in the hope of obtaining further improvement in the above parameters in the series of patients reported here. However, neither clinical nor EEG benefit was noted in the present study and slight transient worsening of the existing neurological deficit occurred in four patients. The observations on cerebral hemodynamic and metabolic effects are discussed below.

CEREBRAL HEMODYNAMIC EFFECTS OF COMBINED PBZ AND PPL

Infusion of PBZ and PPL did not alter HBF in patients studied despite significant fall in CPP. The constancy of CBF despite reduction in CPP indicates continuation of cerebral autoregulatory vasoactivity, despite alpha and beta adrenergic blockade. Furthermore, after combined PBZ and PPL infusion, cerebral vessels were able to both dilate and constrict potently during changes in CPP induced by body tilting. Since the observed autoregulatory responses during body tilting occurred within seconds, it seems likely that other neurogenic rather than metabolic influences maintain cerebral autoregulation after the inhibition of adrenergic control. These findings, therefore, may be taken as additional evidence that neurogenic control of cerebral circulation involves not only alpha and beta adrenergic influences but may be mediated in part by other neurogenic factors which could include dopaminergic, histaminergic, cholinergic and serotoninergic systems.

It seems appropriate to review briefly the evidence for other neurogenic influences on cerebral autoregulation. Originally, dopamine was assumed to be located exclusively in the basal ganglia and to be concerned only with extrapyramidal function. Now, by the use of recently developed histochemical techniques, cortical distribution of dopaminergic nerve terminals has been demonstrated. The effect of exogenously administered dopamine on CSF is diverse; high and low doses cause decrease whereas intermediate doses cause increase. The inhibition of dopamine-induced CBF increases not by PPL but by haloperidol indicates the possible presence of specific dopamine receptors in cerebral blood vessels. Nevertheless, the exact role of the dopaminergic system in CBF control remains to be substantiated.

Recent experiments have demonstrated the existence of specific histaminergic neuronal pathways in brain. In both animals and man, exogenously administered histamine appears to produce dilatation of cerebral vessels and marked increase in CBF. Relevant to the present study, histamine receptors in brain, which are postulated to be present also in cerebral vessels, are unaffected by either alpha or beta adrenergic blockade. Therefore, it seems likely that other neurogenic rather than metabolic influences maintain cerebral autoregulation after the inhibition of adrenergic control. These findings, therefore, may be taken as additional evidence that neurogenic control of cerebral circulation involves not only alpha and beta adrenergic influences but may be mediated in part by other neurogenic factors which could include dopaminergic, histaminergic, cholinergic and serotoninergic systems.

It seems appropriate to review briefly the evidence for other neurogenic influences on cerebral autoregulation. Originally, dopamine was assumed to be located exclusively in the basal ganglia and to be concerned only with extrapyramidal function. Now, by the use of recently developed histochemical techniques, cortical distribution of dopaminergic nerve terminals has been demonstrated. The effect of exogenously administered dopamine on CSF is diverse; high and low doses cause decrease whereas intermediate doses cause increase. The inhibition of dopamine-induced CBF increases not by PPL but by haloperidol indicates the possible presence of specific dopamine receptors in cerebral blood vessels. Nevertheless, the exact role of the dopaminergic system in CBF control remains to be substantiated.

Recent experiments have demonstrated the existence of specific histaminergic neuronal pathways in brain. In both animals and man, exogenously administered histamine appears to produce dilatation of cerebral vessels and marked increase in CBF. Relevant to the present study, histamine receptors in brain, which are postulated to be present also in cerebral vessels, are unaffected by either alpha or beta adrenergic blockade. Therefore, it seems likely that other neurogenic rather than metabolic influences maintain cerebral autoregulation after the inhibition of adrenergic control. These findings, therefore, may be taken as additional evidence that neurogenic control of cerebral circulation involves not only alpha and beta adrenergic influences but may be mediated in part by other neurogenic factors which could include dopaminergic, histaminergic, cholinergic and serotoninergic systems.

It seems appropriate to review briefly the evidence for other neurogenic influences on cerebral autoregulation. Originally, dopamine was assumed to be located exclusively in the basal ganglia and to be concerned only with extrapyramidal function. Now, by the use of recently developed histochemical techniques, cortical distribution of dopaminergic nerve terminals has been demonstrated. The effect of exogenously administered dopamine on CSF is diverse; high and low doses cause decrease whereas intermediate doses cause increase. The inhibition of dopamine-induced CBF increases not by PPL but by haloperidol indicates the possible presence of specific dopamine receptors in cerebral blood vessels. Nevertheless, the exact role of the dopaminergic system in CBF control remains to be substantiated.

Recent experiments have demonstrated the existence of specific histaminergic neuronal pathways in brain. In both animals and man, exogenously administered histamine appears to produce dilatation of cerebral vessels and marked increase in CBF. Relevant to the present study, histamine receptors in brain, which are postulated to be present also in cerebral vessels, are unaffected by either alpha or beta adrenergic blockade. Therefore, it seems likely that other neurogenic rather than metabolic influences maintain cerebral autoregulation after the inhibition of adrenergic control. These findings, therefore, may be taken as additional evidence that neurogenic control of cerebral circulation involves not only alpha and beta adrenergic influences but may be mediated in part by other neurogenic factors which could include dopaminergic, histaminergic, cholinergic and serotoninergic systems.
beta adrenergic blockade. Again, the role of the histaminergic system in the control of CBF has not been defined.

Evidence is also accumulating in favor of a cholinergic influence on CBF control. Histochemical and electron microscopic studies indicate that cholinergic and adrenergic nerve fibers accompany one another in their course along the internal carotid artery, and can be traced to intracranial vessels of arteriolar caliber. Intravertebral injection of acetylcholine in the baboon has also been found to increase CBF.

Serotonergic neurons are located within the midline raphe nuclei of the mesencephalon and upper pons and have both ascending cortical and descending spinal projections. SHT is well known to cause potent cerebral vasoconstriction and CBF reduction, which is also apparently not modified by alpha-adrenergic blockade. Again, the role of serotoninergic neurons in the physiological control of the cerebral circulation is unknown.

Although there is strong pharmacological evidence for the existence of several neurogenic influences (in addition to alpha and beta adrenergic) on the control of the cerebral circulation, it should be borne in mind that morphological evidence for neuronal systems such as the above actually supplying intraparenchymatous cerebral vessels is scanty and controversial.

If, indeed, in the physiological state there exists balanced neurogenic control of the cerebral circulation, then perhaps such balance may be disturbed in ischemic brain. This may be one explanation for the observed paradoxical responses to induced hypertension or hypotension which indicate excessive cerebral vasoconstriction or dilatation, respectively, in some patients. The frequency of such responses was increased after combined alpha and beta receptor blockade, which therefore appears to further disrupt the perhaps tenuous balance of CBF control which still functions in ischemic brain.

Other factors which need to be considered in the pathogenesis of disordered cerebrovascular control include ischemic neuronal damage causing degeneration of presynaptic nerve fibers which results in hypersensitivity of denervated post-synaptic receptor sites (denervation hypersensitivity). This factor plus excessive extraneuronal release of vasoactive neurotransmitters in ischemic brain might well explain the paradoxical responses observed in the current series of patients. This hypothesis raises a second possibility that the increased number of paradoxical responses observed after administration of PPL and PBZ might be due to enhanced neurotransmitter release from other neuronal systems in response to PBZ and PPL. This view is supported by biochemical data pertinent to neurotransmitter function obtained in the present patient group and which will therefore be discussed in this section.

Increase in CSF 5HIAA as well as a less significant increase in CSF HVA levels suggest increased neuronal SHT and DA synthesis or release after PBZ and PPL. Perhaps paradoxical cerebral vasoconstrictor responses to induced hypertension could in part be attributed to increased SHT turnover and paradoxical cerebral vasodilatation responses to increased DA turnover. The mechanisms by which this takes place are complex and possibly involve other putative neurotransmitters. The biphasic tyrosine uptake from cerebrovenous blood, also recorded in the patients studied, confirms stimulation of catecholamine turnover. This probably

---

**TABLE 6** Effect of Combined PBZ and PPL Infusion on Arterial, Cerebral Venous and CSF Concentrations of Cyclic AMP (pmole/ml)

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>V</th>
<th>A-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state</td>
<td>22 ± 13</td>
<td>27 ± 14*</td>
<td>-5 ± 3</td>
</tr>
<tr>
<td>(N = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After infusion</td>
<td>20 ± 11</td>
<td>21 ± 9</td>
<td>-1 ± 4†</td>
</tr>
<tr>
<td>(N = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant as compared with arterial value.
†Significant as compared with steady state value.

A = mean ± SD.

N = number of cases.
results from complex change in feedback-mediated synthesis control brought about by post-synaptic and perhaps putative presynaptic receptor blockade by PBZ and PPL. Increased CSF 5HIAA may be the result of similar alteration in SHT turnover caused by PBZ blockade of serotonin receptors or else may be secondary to SHT release promoted by catecholamine overflow from synaptic clefts of catecholamine neurons which have been subjected to post-synaptic receptor blockade. Unfortunately in the present study, lack of data concerning specific NE metabolites in CSF allows no informed comment on alteration in NE turnover.

Cyclic AMP release into cerebral venous blood was observed in the total series of patients studied. This has been recorded in a separate series of patients as well as elevation of cyclic AMP in the CSF. These findings are thought to indicate extracellular accumulation of cyclic AMP due either to increase in neuronal membrane permeability or to increased neurotransmitter release in ischemic brain. PBZ and PPL abolished cyclic AMP release into cerebral venous blood in the present study. This may be in part accounted for by improvement in neuronal membrane function or more likely to the inhibition of intraneuronal cyclic AMP formation caused by blockade of adrenergic receptor sites. Despite reduction of CSF cyclic AMP levels in a few patients, the strong tendency (0.05 < P < 0.1) for increase of mean change in cyclic AMP levels after PBZ and PPL would support the former concept.

Although angiotensin has been postulated as a factor which may promote cerebral vasoconstriction, reduction in arterial blood levels, which is explained by the effect of PPL on beta-adrenergic receptors in the juxtaglomerular apparatus, makes it unlikely that this agent could play any convincing role in the production of the paradoxical vasoconstrictor responses observed in the present study.

Increase in mean CSF pressure after alpha and beta adrenergic blockade seems best accounted for by increased CSF production, since CBF and intracranial venous pressure were unchanged. In a previous study, PBZ alone significantly increased CSF pressure; PPL produced no change. The work of Edvinsson et al. has suggested that sympathetic innervation to the choroid plexus exerts an inhibitory action on CSF production. CSFP increase after PBZ and PPL observed in the present study would appear to lend some support to the concept that CSF production by the choroid plexus may in part be inhibited by alpha-adrenergic influences.

SYSTEMIC METABOLIC EFFECTS OF PBZ AND PPL

Increase in arterial glucose levels has been reported previously after administration of either PBZ or PPL and is reputed to be of hepatic origin. However, other reports also exist to suggest a hypoglycemic effect of PPL, it being well known that insulin requirement is reduced in diabetics receiving PPL therapy. It seems that hepatic glycogenolysis may be balanced by enhanced glycogen storage in muscle since adrenergic blockade results in phospholipase inhibition. This latter finding is supported by diminished arterial blood lactate levels after PBZ and PPL in the present series of cases.

Both alpha and beta adrenergic receptors are present in human adipose tissue, although receptors respond in different ways. Beta-receptor blockade decreases lipolysis so that plasma concentrations of free fatty acids (FFA) and glycerol become reduced. In contrast, after alpha-receptor blockade, plasma FFA and glycerol levels increase. Results reported here suggest predominant beta-adrenergic influence on lipolysis since blood levels of triacylglycerols and glycerol became decreased.

CEREBRAL METABOLIC EFFECTS OF PBZ AND PPL

PBZ and PPL infusion caused a significant shift toward anaerobic metabolism as evidenced by increase in HMIGI, HG:O ratio and CMR lactate. Although this was accompanied by a decrease in HMIO2, it seems unlikely that increased anaerobic metabolism occurs as a result of a cerebral "Pasteur effect" since (1) oxygen content increased in arterial blood (no hypoxemia) (fig. 8), (2) CBF remained constant (no ischemia) and (3) CVPo2 was unaltered (no hypoxia), the last parameter being the best available indicator in the present study of unaltered tissue Po2. Furthermore, PPL shifts the hematoglobin-oxygen dissociation curve of arterial blood to the right since, by the "Bohr effect," should improve oxygen delivery to brain tissue. Enhanced cerebral anaerobic glycolysis after PBZ and PPL therefore requires further explanation.

PPL has generally been found to reduce cerebral lactate levels, possibly by causing inhibition of brain phosphofructokinase activity. On the other hand, PBZ has been found to elevate cerebral lactate levels in similar studies. Increase in HMI lactate in the present series of patients might therefore be ex-

![Graph](image-url)
plained by a predominant effect of PBZ on cerebral energy metabolism. On the other hand, serotonin has been found to stimulate glycolysis in brain tissue by direct activation of hexokinase activity and therefore may in part drive glycolytic activity after alpha and beta receptor blockade by PBZ and PPL. The direct influence of cyclic AMP to glycolysis by modulating phosphofructokinase activity is still controversial, and to date no evidence has been available indicating that a specific neurotransmitter stimulates glycolysis by direct activation of phosphofructokinase activity.

Exchange of high molecular weight compounds such as phospholipids and triacylglycerols across the blood-brain barrier as evidenced by the measurement of significant cerebral A-V differences must, of course, imply blood-brain barrier damage, and interpretation of such results in terms of any relation to cerebral tissue metabolism must be interpreted with caution. In the patients studied increased release of triacylglycerols into cerebral venous blood was observed after PBZ and PPL. It can only be speculated that this finding is in accord with inhibition of norepinephrine-induced neuronal lipid breakdown perhaps stimulated in part by abnormal norepinephrine release in ischemic brain.

It seems unlikely that re-esterification of glycerol with free fatty acids could serve as an additional explanation for the observed triacylglycerol release, since cerebral A-V differences for glycerol remained unaltered. Moreover, increased neuronal 5HT release after PBZ and PPL suggested in the present study may, on the basis of evidence from animal studies, inhibit re-esterification of free fatty acids with glycerol.

In conclusion, these results have been obtained from patients with stroke and for obvious reasons, no control group is available. The reader should bear this caution in mind when evaluating the results. Study of cerebral hemodynamics before and after PBZ and PPL suggests a functional balance between other neurogenic influences such as serotoninergic, dopaminergic, cholinergic and probably histaminergic systems as well as alpha and beta adrenergic systems in the control of cerebral circulation. Imbalance of such controlling factors in ischemic brain may lead to excessive cerebral vasoconstriction or vasodilatation in response to induced hypertension or hypotension, respectively. PBZ and PPL enhance such responses perhaps by increasing neuronal 5HT and DA release. Further shift toward cerebral anaerobic glycolysis may occur in ischemic brain after PBZ and PPL. No improvement in EEG was noted in the patients studied and worsening of neurological deficit was found in a small number of cases. Combined therapy with PBZ and PPL does not appear to be beneficial in the therapy of patients with recent stroke.

References

APHASIA IN ACUTE STROKE/Brust et al.

SUMMARY Previous surveys of stroke populations have offered only cursory information on language disturbance and, conversely, few surveys of aphasic populations have dealt exclusively with stroke or with acute phenomena. This paper describes aphasia in 850 acute stroke patients consecutively registered by the Harlem Regional Stroke Program, of whom 177 (21%) were aphasic; of these, nine were of Broca's type, 24 were of Wernicke's type, 14 were anomic, or with acute phenomena. This paper describes aphasia in 850 acute stroke patients, of whom 177 (21%) were aphasic; of these, nine were of Broca's type, 24 were of Wernicke's type, 14 were anomic, 10 were conduction, seven were of "isolation" type, and 107 were "mixed." An unexpected finding was a significant over-representation of men among the nonfluent aphasics.

During the following four to 12 weeks, 12% of fluent aphasics died, and 12% remained moderately or severely impaired; among survivors, aphasia improved in 74%, and in 44% it cleared completely. During the same period, 32% of nonfluent aphasics died, and 34% remained moderately or severely impaired; among survivors, aphasia improved in 52%, and in only 13% did it clear completely. In both fluent and nonfluent groups, hemiparesis and/or visual field cut were associated with poor prognosis.

Methods

From 1971 through 1973, 850 patients were admitted to Harlem Hospital with the diagnosis of acute stroke. Criteria for inclusion in the registry of the Harlem Regional Stroke Program have been previously described. Upon admission the patient was examined by members of the Medical House Staff, plus a neurologist consultant. In addition, 12 to 48 hours and then at periodic intervals an examination was performed by a member of the Stroke Program Team and recorded on standardized forms. The data of this report are
Influence of adrenergic receptor blockade on circulatory and metabolic effects of disordered neurotransmitter function in stroke patients.
J S Meyer, Y Miyakawa, K M Welch, Y Itoh, N Ishihara, E Chabi, J Nell, K Bartosh and A D Ericsson

Stroke. 1976;7:158-167
doi: 10.1161/01.STR.7.2.158

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/7/2/158

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/