The Influence of Nonrespiratory Alkalosis on Cerebral Blood Flow in Cats

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Abstract:
Cerebral blood flow was measured with the 133Xenon clearance method during short-lasting (20 minutes) and more prolonged (90 minutes) infusions of Na2CO3 solutions in anesthetized cats under controlled ventilation. The infusion protocol was regulated so as to produce a given increase in the plasma [HCO3] in the first 15 minutes, followed by a constant high plasma level for the rest of the infusion period. A high Paco2 level was induced before and at the end of the infusion, when prolonged infusions were made. The results indicate that, in acute experiments (20 minutes), an increase in plasma [HCO3] of 14 mEq/l does not influence CBF. During more prolonged infusions (90 minutes), an increase of 12 mEq/l produces a reduction of CBF and an increase in the CSF [HCO3]. These changes are more pronounced when the increase in plasma [HCO3] is more marked (18 mEq/l).

Additional Key Words
metabolic alkalosis
hypercapnia
133Xenon

There is conflicting evidence concerning the acute effects of acids and alkalis on the cerebral blood vessels. In early experiments, it was shown that the caliber of pial vessels or the cerebral blood flow increased during metabolic acidosis and decreased during metabolic alkalosis, but in later experiments this was not confirmed; even opposite effects were reported by several authors.

During chronic metabolic changes in the acid-base balance, the cerebral blood flow (CBF) at a given arterial Paco2 level (Paco2) was found to be higher in acidosis and lower in alkalosis compared with the normal condition, and these changes have been correlated with alterations of the cerebrospinal fluid (CSF) pH.

The present experiments were performed to investigate further the influence of the magnitude, time course, and duration of metabolic changes in plasma pH on CBF in anesthetized cats.

Methods
The experiments were conducted on adult cats. Repeated small doses of thiopental were given intravenously during the surgical preparation. Thereafter, the animals were paralyzed with gallamine-HCl (Flaxedil®, 5 mg per kilogram per hour) and mechanically ventilated with a gas mixture containing 67.5% N2O, 25% O2 and 7.5% N2. To alter the Paco2, N2 was replaced by CO2 without altering the % N2O and O2 in the inspired gas mixture. Body temperature was kept approximately constant by means of a heating pad, eventually supplemented by radiant heating. The methods used for the determination of the acid-base parameters in arterial blood plasma and in cerebrospinal fluid were previously described. In a few experiments, plasma osmolarity was determined by the freezing point method with a Fiske osmometer. Chloride was determined in cerebrospinal fluid with a coulometric-amperometric titration method.

MEASUREMENT OF CBF
Cerebral blood flow was measured with the 133Xenon clearance method. About 0.25 ml of 133Xenon solution (0.5 mCi) was injected into the carotid system in five seconds via a small polyethylene catheter inserted into the carotid artery via the cut thyroid artery. The washout of the radioactive substance was recorded for at least ten minutes by means of a single collimated scintillation detector placed over the skull in the temporal region, and an amplifier, pulse height analyzer and linear ratemeter assembly as previously described. The skin and muscles on the skull were removed in order to minimize the influence of isotope uptake in extracranial tissue on the records. A 0.5-second time constant was used to record the first two minutes of clearance, and a 1.5-second time constant was used thereafter. The CBF was calculated in milliliters per 100 gm-minute according to the stochastic method. By this method (the "height over area" method), mean CBF is calculated from the formula:

\[ CBF = \frac{H - H_{10}}{100} \cdot \lambda \cdot 100 \text{ ml} \]

where H is the initial height of the clearance curve in counts/minute, H10 the height of the curve in counts/minute following ten minutes of clearance, \( A_{10} \) (corr) the total number of counts during the first ten minutes of clearance corrected for background, recirculation, and rest activity from a previous injection, and \( \lambda \) the partition coefficient for 133Xenon between brain and blood. We found that this partition coefficient for whole brain approximates unity in the cat which agrees with the observations in dog and man.
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Experimental Procedure
The cats were ventilated with 0% CO₂ for one hour before the beginning of each study. When the ventilation was changed in the course of an experiment, it was done at least 20 minutes before a CBF measurement. The ventilation was adjusted so as to obtain a Paco of approximately 30 mm Hg (26 to 34 mm Hg) in control conditions, which is similar to values obtained in conscious cats. In these control conditions was similar to the values obtained by Swanson and Rosengren.

In a first series of experiments on six cats, the influence of acute changes in the plasma [HCO₃⁻] was investigated. A first CBF measurement was made during ventilation with 0% CO₂, followed by a second measurement during ventilation with 7.5% CO₂. Ventilation then was kept on 7.5% CO₂ and an I.V. infusion of Na₂CO₃ (0.30 M) was started and maintained for 30 minutes. A third CBF measurement was made 20 minutes after the beginning of the infusion.

In a second series of experiments on 24 cats, the influence of more prolonged changes in the plasma [HCO₃⁻] was investigated. A first CBF measurement was made during ventilation with 0% CO₂, followed by a second measurement during ventilation with 5% CO₂. The cats then were ventilated again with 0% CO₂ and an intravenous infusion of Na₂CO₃ or of NaCl was started and maintained for 90 minutes. CBF was measured 30, 60 and 90 minutes after the start of the infusion, the last measurement being made under 5% CO₂ ventilation. CSF was sampled during ventilation with 0% CO₂ immediately after the first and fourth CBF measurements.

During the infusion of the Na₂CO₃ solution, the infusion rate was regulated so as to produce a given change in the plasma [HCO₃⁻] in the first 15 minutes and to maintain a constant plasma level for the rest of the infusion period. The same infusion protocol was applied to cats infused with NaCl and the toxicity of these solutions (0.29 or 0.37 M NaCl) was equal to that of the Na₂CO₃ solutions (0.23 or 0.30 M Na₂CO₃). The total fluid volume infused in the second series of experiments amounted to approximately 18 ml per kilogram. Solutions were warmed to 38°C in order to prevent cooling of the cat during the infusion.

To compare the results obtained before and after an infusion in each experimental group, a statistical analysis was done with the paired t-test.

In some cats, the permeability of the cerebral vessels was studied at the end of the experiment. Evans blue dye (4 ml per kilogram of a 2% solution made isotonic by the addition of NaCl) was injected intravenously during ventilation with 5% CO₂. The cats were killed 45 minutes after the infusion of the dye. The head was perfused in situ, first with 0.9% NaCl, then with 10% formalin, and the brain was removed and inspected macroscopically for blue staining after peeling of the arachnoid membrane.

Results

INFLUENCE OF ACUTE CHANGES IN THE PLASMA [HCO₃⁻]
The influence of acute changes in the plasma [HCO₃⁻] on CBF was investigated in six cats. The results of these experiments are presented in table 1. CBF increases markedly when plasma pH is altered by the administration of 7.5% CO₂. However, when an identical but inverse alteration in blood pH is acutely (20 minutes) induced at constant high Paco, by increasing the plasma [HCO₃⁻] through an infusion of Na₂CO₃ (0.30 M), CBF is not different from the preinfusion value at this Paco level.

INFLUENCE OF PROLONGED CHANGES IN THE PLASMA [HCO₃⁻]
In order to study the influence not only of time but also of the magnitude of the increase in plasma [HCO₃⁻] on CBF, two series of experiments were performed with intravenous infusions of either a 0.23 M or a 0.30 M Na₂CO₃ solution.

The results obtained in this series of experiments on ten cats are presented in figure 1. Two different Paco levels were studied before and during the infusion of Na₂CO₃. Plasma actual [HCO₃⁻] was increased by about 10 mEq/l (from 14 ± 0.5 to 24 ± 0.5 mEq/l) 15 minutes after the beginning of the infusion; it increased slightly further to 26 ± 0.5 mEq/l 15 minutes later, and was then constant at this level throughout the rest of the infusion period. The mean increase in blood pH was 0.23 (from 7.29 ± 0.01 to 7.52 ± 0.02). At a Paco level of about 30 mm Hg, 60 minutes after the beginning of the Na₂CO₃ infusion, CBF was not significantly altered with respect to the control value (from 43 ± 5 to 40 ± 5 ml/100 gm · minute). However, at a Paco level of about 48 mm Hg, 90 minutes after the beginning of the infusion, CBF was significantly (0.02 < P < 0.05) depressed with respect to the control value at the same Paco, (from 115 ± 10 to 93 ± 10 ml/100 gm · minute). The [HCO₃⁻] in CSF was significantly increased (P < 0.001) 60 minutes after the start of the infusion (from 23.5 ± 0.5 to 23.5 ± 0.5 mEq/l). Arterial blood pressure was generally unchanged during the experiment. Chloride

<table>
<thead>
<tr>
<th>% CO₂</th>
<th>Infusion</th>
<th>Paco₂ (mm Hg)</th>
<th>Actual [HCO₃⁻] (mEq/l)</th>
<th>pH</th>
<th>CBF (ml/100 gm · minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>—</td>
<td>26 ± 3</td>
<td>11 ± 1</td>
<td>7.22 ± 0.02</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>7.5</td>
<td>—</td>
<td>67 ± 3</td>
<td>16 ± 1</td>
<td>7.00 ± 0.02</td>
<td>115 ± 15</td>
</tr>
<tr>
<td>7.5</td>
<td>Na₂CO₃</td>
<td>66 ± 3</td>
<td>30 ± 1</td>
<td>7.27 ± 0.02</td>
<td>115 ± 15</td>
</tr>
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*Mean values ± SEM obtained in six cats.
in CSF and plasma osmolarity were determined in two cats before and 60 minutes after the beginning of the intravenous infusion. \([\text{Cl}^-]\) in CSF was unaltered while the plasma osmolarity increased slightly (from 318 to 327 mOsm/l). On visual inspection the brains were not found to be colored by the Evans blue administration.

**Infusions With Na\(_2\)CO\(_3\) — 0.30 M**

The results obtained in this series of experiments on six cats are presented in figure 2. The experimental protocol was similar to that of the previous experiments. Plasma actual \([\text{HCO}_3^-]\) was increased by about 14 mEq/l (from 14 ± 1 to 28 ± 1 mEq/l) 15 minutes after the beginning of the infusion; it increased further to 33 ± 1 mEq/l 15 minutes later, and was then constant at this level throughout the rest of the infusion period. The mean increase in blood pH was 0.31 (from 7.25 ± 0.01 to 7.56 ± 0.02). At a Paco\(_2\) level of about 34 mm Hg, 60 minutes after the beginning of the Na\(_2\)CO\(_3\) infusion, the CBF was significantly (0.02 < P < 0.05) depressed with respect to the control value (from 46 ± 4 to 37 ± 2 ml/100 gm · minute). At a Paco\(_2\) level of about 50 mm Hg, 90 minutes after the beginning of the infusion, the depression of CBF (from 130 ± 15 to 80 ± 10 ml/100 gm · minute) was highly significant (0.001 < P < 0.01) with respect to the control value at the same Paco\(_2\). The \([\text{HCO}_3^-]\) in CSF was significantly increased (P < 0.001) 60 minutes after the start of the infusion (from 20.6 ± 0.6 to 26.7 ± 0.7 mEq/l). Arterial blood pressure was generally unchanged during the experiment. Chloride in CSF and plasma osmolarity were determined in three cats before and 60 minutes after the beginning of the Na\(_2\)CO\(_3\) infusion. \([\text{Cl}^-]\) in CSF decreased slightly (from 147 to 136 mEq/l), while the plasma osmolarity increased from 315 to 348 mOsm/l. On visual inspection, the brains were

**FIGURE 1**

Influence of an infusion of a 0.23 M Na\(_2\)CO\(_3\) solution on mean cerebral blood flow (CBF) in cats. Paco\(_2\), arterial Paco\(_2\); \([\text{HCO}_3^-]\) — actual bicarbonate concentration in arterial blood plasma (white bars), and bicarbonate concentration in CSF (hatched bars). The mean values ± SEM obtained on six cats are presented for the different parameters 40 minutes and 10 minutes before, and 15, 30, 60 and 90 minutes after the beginning of the Na\(_2\)CO\(_3\) infusion. The animals were ventilated for 30 minutes with 5% CO\(_2\), starting 30 minutes before and 70 minutes after the beginning of the infusion.

**FIGURE 2**

Influence of a 0.30 M Na\(_2\)CO\(_3\) infusion on CBF in cats. The parameters are shown in the same conditions and at the same time intervals as in figure 1. Mean values ± SEM obtained on ten cats.
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not found to be colored by the Evans blue administration.

INFLUENCE OF HYPERTONIC NaCl
In order to study the influence of the general experimental procedure, control experiments were carried out with a 0.29 M NaCl solution. The experimental protocol was similar to that of the experiments with prolonged infusions of Na₂CO₃ (cf. methods), and the mean values ± SEM obtained on six cats are shown in figure 3.

Plasma actual [HCO₃⁻] (15 ± 1 mEq/l), blood pH (7.32 ± 0.01), CSF [HCO₃⁻] (20.3 ± 0.5 mEq/l) and arterial blood pressure (15 ± 0.5 cm Hg) were unaltered during these experiments. Also, CBF was not changed at the end of the infusion period, either at a Paco₂ level of about 30 mm Hg (40 ± 2 and 42 ± 3 ml/100 gm • minute) or at a Paco₂ level of about 50 mm Hg (130 ± 14 and 128 ± 15 ml/100 gm • minute).

Similar results were obtained with a 0.37 M NaCl solution in two cats.

Discussion
Bronk and Gesell reported that intravenous injections of sodium carbonate and sodium bicarbonate solutions increased blood flow in the carotid arteries of anesthetized dogs, while other investigators, working on perfused brain, or using a cranial window, claimed that alkalosis constricted the cerebral blood vessels. The conflicting evidence pertains to the more recent studies using more direct and less traumatic methods for measuring CBF and where secondary influences such as changes in blood Paco₂ and in arterial blood pressure were carefully controlled. Differences in magnitude, time course and duration of the changes in plasma pH, and differences in Paco₂ levels during the experiments might be partly responsible for the divergent results.

In the present experiments, the effect of an increase in plasma [HCO₃⁻] was investigated during short-lasting (20 minutes) and more prolonged (90 minutes) infusions of Na₂CO₃ solutions under controlled ventilation. Hypercapnia was induced before and at the end of the infusion. During prolonged infusions, the Paco₂ was kept at a normal level (30 to 35 mm Hg) during the first 70 minutes of the infusion to avoid the effect of a sustained increase in the Paco₂ on CBF and CSF [HCO₃⁻]. An acute increase of 14 mEq/l in plasma [HCO₃⁻] does not influence the CBF response to hypercapnia (table 1). However, when an even smaller increase (12 mEq/l) of the plasma [HCO₃⁻] is sustained for 90 minutes, the CBF response to hypercapnia appears to show a decrease of 20% (fig. 1). This effect is still more marked (40% reduction of CBF) when the increase in the plasma [HCO₃⁻] is more pronounced (18 mEq/l) (fig. 2). In normocapnia CBF was practically not influenced when the plasma [HCO₃⁻] was increased by 12 mEq/l for 60 minutes (fig. 1). It showed a 20% reduction when the plasma [HCO₃⁻] was increased by 18 mEq/l (fig. 2). The blood-brain partition coefficient (A) for ¹³³Xenon was not corrected for changes in hematocrit, since this parameter diminished maximally by 0.04 during infusions of 0.30 M Na₂CO₃. Such a change would increase A by about 5%, which would not influence the interpretation of the results.

The lack of effect on CBF of the carbonate infusion in the acute experiments contrasts with the depressive influence of more prolonged infusions. The results of the acute experiments are in agreement with those of Schmidt and Pierson, Lambertsen et al., and of Harper and Bell. As in previous experiments on rats, the cerebral vasodilatation which occurs on raising the arterial Pco₂ is clearly dissociated from the concomitant fall in blood pH.

The decreased CBF during prolonged infusions of Na₂CO₃ solutions cannot be explained by the general
experimental protocol (anesthesia, time) as indicated by control experiments with NaCl infusions (fig. 3).

A current hypothesis proposes that the cerebrovascular resistance is influenced by pH changes somewhere in the brain tissue, probably in the extracellular fluid of arterial smooth muscle.12, 27 During chronic metabolic changes in the acid-base balance, CBF at a given arterial Paco₂ level was found to be higher in acidosis and lower in alkalosis compared with the normal conditions.10, 11 and these changes have been correlated with alterations of the pH in CSF and in the cerebral interstitial fluid.11-13

The mechanisms of [HCO₃⁻] exchange between blood and CSF are still unknown, and different observations indicate that CSF [HCO₃⁻] is largely independent of blood [HCO₃⁻].14-26 The increase in the CSF [HCO₃⁻] in the present experiments, 60 minutes after the beginning of the Na₂CO₃ infusion (figs. 1 and 2) was rather unexpected since acute metabolic alterations in plasma cause little change of total CO₂ in the CSF in dogs28 unless blood is made strongly acidic or alkalotic during several hours.29, 30 The inhalation of 5% CO₂ for 30 minutes between the two CSF samplings cannot explain the increase, as indicated by the control experiments; neither was it the reflection of a general concentration of ions in the CSF due to the administration of hypertonic solutions, since the concentration of other ions, such as chloride, did not increase. The blood-CSF barrier for [HCO₃⁻] may be more permeable in the cat than in other species, or the increase in CSF [HCO₃⁻] might be favored by the infusion protocol (sudden increase in plasma [HCO₃⁻] and constant high plasma level) and by the increase in plasma tonicity (10%) especially with the 0.30 M Na₂CO₃ solutions. Rapoport et al.32-35 obtained an increased permeability of the blood-brain barrier by topical application or intracarotid injection of hypertonic solutions, but the experimental situation cannot be directly compared, and the brains were not colored by the dye in the present experiments.

Whatever the underlying mechanism, the increased CSF [HCO₃⁻] suggests an increase of the [HCO₃⁻] of the cerebral interstitial fluid. This would imply a more alkaline pH at any Paco₂ level, and could explain the decrease in CBF during prolonged infusions of Na₂CO₃ in the light of the pH hypothesis for CBF regulation.

The effect of a prolonged Na₂CO₃ infusion on CBF seems more marked during hypercapnia than during normocapnia. This could be merely another illustration of the time dependency of this phenomenon, since the hypercapnic point was studied 30 minutes later than the normocapnic point. On the other hand, the vasoconstrictive effect of an alkalinization also might be less marked at the lower end of the Paco₂ response curve for CBF.28

A vasoconstrictive effect of alcalis was already reported in earlier literature,11, 23 but these results are difficult to evaluate since the magnitude and time course of the changes in the acid-base balance were not clearly defined: Paco₂ and arterial blood pressure were not always kept constant and the integrity of the blood-brain barrier could have been compromised during brain perfusion experiments or after craniotomy and opening of the dura.

The increased CBF during metabolic alkalosis reported by some authors12-29 contrasts with the results of the present study. Large infusions of concentrated solutions must be used to produce an important sustained increase of the plasma [HCO₃⁻] and CBF could be increased by factors unrelated to pH in this type of experiment such as dilutional anemia (especially during hypocapnia), decreased blood viscosity, or plasma hypertoncity.30-32 Compensatory changes in respiration with concomitant alterations in the Paco₂ might further favor an increase in CBF during NaHCO₃ infusions when ventilation is not controlled.1, 7 In our experiments with controlled Paco₂ such an increase of CBF during infusion metabolic alkalosis was not observed.

References

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