Brain pH Responses to Acetazolamide and Hypercapnia in Cats

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Abstract

The involvement of increased brain tissue CO_2 tension in acetazolamide-induced brain acidosis was investigated by comparing the brain pH response to acetazolamide with that to hypercapnia. CO_2 and pH sensors were placed bilaterally into cerebral white matter to 15 mm depth in cats. Group 1 cats (n = 9) breathed spontaneously, and in situ brain tissue P_{CO_2} and pH (Pb_{CO_2} and pHb) were measured after intravenous acetazolamide administration (20 mg/kg). Group 2 cats (n = 9) were paralyzed and ventilated mechanically, and the changes of pHb were investigated by adjusting the ventilation to maintain the same Pb_{CO_2} values as in the acetazolamide-treated group. Pb_{CO_2} changes were not significantly different between the two groups. However, pHb responses were quite different: the fall in pHb was progressive in Group 1 but transient in Group 2. Brain acidosis after acetazolamide administration is not due to the rise in brain tissue CO_2 tension.

Key words: carbonic anhydrase, acetazolamide, pH regulation, cerebrovascular diseases

Introduction

Measurements of regional cerebral blood flow (CBF) have been used to evaluate the hemodynamic significance of ischemic cerebrovascular disease. Assessment of the capacity to increase CBF in response to vasodilators such as CO_2 or acetazolamide is another way of measuring cerebral circulatory reserve.

Acetazolamide, a selective inhibitor of carbonic anhydrase, is more easily administered to patients with cerebrovascular disease than CO_2, because it has little influence on the cardiopulmonary system.[11,27] Acetazolamide increases the CBF remarkably and induces an increase in both brain tissue P_{CO_2} (Pb_{CO_2}) and carbonic acidosis, but the mechanisms for these effects have remained obscure. Moreover, there is a dissociation between the changes in Pb_{CO_2} and brain tissue pH (pHb); the fall in pHb is large despite the rise in Pb_{CO_2} being only slight after acetazolamide administration.[4,28,30] The effects of acetazolamide on the acid-base balance might occur via a direct inhibition of carbonic anhydrase local-ized on brain cells.[4,30] However, the effects may be due to carbonic anhydrase inhibition in red blood cells (RBCs),[21,22,31] because acetazolamide injected intravenously crosses the blood-brain barrier (BBB) slowly,[21,23,29] whereas both Pb_{CO_2} and pHb change rapidly immediately after intravenous administration of acetazolamide.[4,10,21,22,28] If these effects are caused only by disturbance of the CO_2-carrying capacity of RBCs, the pH responses to both acetazolamide and hypercapnia should be similar if the time course of Pb_{CO_2} is similar.

The recent development of the ion-sensitive field-effect transistor (ISFET) allows the measurement of P_{CO_2} and pH in situ.[7,25] In animal and clinical experiments, catheter-tip CO_2 and pH sensors based on ISFET technology have been successfully used to monitor continuously in situ P_{CO_2} and pH in blood and tissues.[18,25] The present study investigated whether acetazolamide-induced brain acidosis is due to the concomitant rise in brain tissue CO_2 tension.

Materials and Methods

Twenty-two cats of both sexes (body weight 3.4 ± 0.3 kg, mean ± SD) were sedated with an in-

traperitoneal injection of 120 mg ketamine. Anesthesia was maintained by continuous infusion of ketamine (200 mg in 10 ml physiological saline) delivered at 2 ml/hr via a femoral venous catheter. The animals had miotic eyes and salivation during the measurements. Rectal temperature was monitored and kept at 38°C by means of a heating table. Arterial and venous catheters were inserted so that arterial P_{CO_2} (Pa_{CO_2}) could be monitored continuously and drugs could be infused. The animals were fixed to a stereotactic cradle, and a midline scalp incision was made after local anesthesia with 1% lidocaine. After the scalp was retracted, two holes of 0.5 cm diameter were drilled bilaterally through the cranium with a burr drill. Hemostasis was achieved with cauterization and bone wax. The centers of the holes were 1.0 cm anterior from the ears and 1.0 cm lateral from the midline. The exposed dura was coagulated and incised.

CO$_2$ and pH sensors (CO$_2$ sensor, CO-1035; pH sensor, pH-2135; Nihon Kohden, Tokyo) used catheter-tip electrodes which contained the pH-ISFET. The CO$_2$ sensor was coated with silicone, and the pH sensor was encapsulated in the end of a nylon tube. These CO$_2$ and pH sensors can measure continuously in situ P_{CO_2} and pH, respectively, in blood and other tissues.[18,25] The pH sensor reveals rapid responses to acidosis and alkalosis, and the response time of the CO$_2$ sensor is 2 minutes for a 90% change in CO$_2$ tension.[25] The pH sensor was calibrated at 37°C with a standard phosphate buffer of pH 7.27, and the CO$_2$ sensor was calibrated at 37°C with sterile P_{CO_2} standard solutions of 36 and 86 mmHg. The baseline drift of the CO$_2$ sensor was less than 2 mmHg during 5 hours of measurements.[18] The CO$_2$ and pH sensors were inserted bilaterally to 15 mm depth from the cortical surface in the center of the holes. Another CO$_2$ sensor was inserted via a femoral arterial catheter to measure Pa_{CO_2} continuously. pH/P_{CO_2} monitors (KR-5000; Nihon Kohden) were used to record the output of the CO$_2$ and pH sensors. Respiratory rate was monitored by the impedance method and averaged every 10 seconds, and heart rate was determined from the electrocardiogram.

Two groups of cats were studied. The first (Group 1) was designed to study the effects of acetazolamide and the second (Group 2) to study those of hypercapnia. Group 1 animals (n = 9) were allowed to breath spontaneously for at least 30 minutes to let all parameters stabilize. At time 0 (control), after determination of all steady-state values, they received a bolus injection of 20 mg/kg acetazolamide dissolved in physiological saline (at a concentration of 100 mg/ml) via a femoral catheter. During the next 60

minutes, the animals remained in the cradle to monitor the parameters, and in situ Pb_{CO_2} and pHb were measured continuously. Group 2 animals (n = 9) underwent tracheotomy and muscle paralysis was achieved with intravenous pancuronium (1.0 mg/kg/hr). They were mechanically ventilated with air with a Harvard respirator (model 665d; Harvard Apparatus, South Natick, Mass., U.S.A.). Pb_{CO_2} was controlled by mechanical ventilation to maintain the mean Pa_{CO_2} value at that measured during the pre-acetazolamide period in Group 1 animals. Then, by reducing the rate and depth of respiration, Pa_{CO_2} was elevated to the mean Pb_{CO_2} value measured after acetazolamide injection within 10 minutes to reflect the Pb_{CO_2} change, because hypoxemia is not induced by hypercapnia[20,33] and the P_{CO_2} gradient between the brain and arterial blood is constant.[16] The mechanically induced Pa_{CO_2} elevation was maintained for more than 60 minutes. All parameters were recorded every 10 seconds by a programmable data logger (7V07; NEC San-Ei, Tokyo).

The obtained data were averaged over 1 minute (6 points) in each animal and analyzed using the Statview statistical package (Abacus Concepts). All values are reported as means ± SE. Within each group, significant differences between time points were determined by one-way analysis of variance followed by Fisher's least significance test. For intergroup comparison of Pb_{CO_2} values, two-tailed unpaired t tests were applied. Statistical significance was taken as a p value of <0.05.

Results

Satisfactory recordings of Pa_{CO_2}, Pb_{CO_2}, and pHb were obtained in 18 of 22 cats. The results in other animals, which developed bleeding at some point in the study, were discarded. The effects of acetazolamide and hypercapnia on Pa_{CO_2}, Pb_{CO_2}, and pHb are summarized in Table 1.

The changes in Pa_{CO_2}, Pb_{CO_2}, and pHb are illustrated by the representative electrode tracings from a Group 1 animal (Fig. 1). Acetazolamide administration was always followed by a rapid rise in Pb_{CO_2}, as well as by a concomitant fall in pHb. Such Pb_{CO_2} changes always reached a steady-state value by 20 minutes after drug administration, and always persisted for at least 40 minutes. The mean Pb_{CO_2} value increased by 25.3 ± 5.6 mmHg at 60 minutes after acetazolamide administration. In contrast, the fall in pHb gradually progressed during the measurements. pHb decreased by 0.20 ± 0.04 pH in 60 minutes. Pa_{CO_2} showed a transient slight rise immediately after acetazolamide administration and then decreased gradually, reaching a steady state at 10 minutes after

Table 1 Effects of acetazolamide and hypercapnia on Pb_{CO_2} and pHb

Time (min)	Acetazolamide			Hypercapnia		
	Pb_{CO_2} (mmHg)	pHb	Pa_{CO_2} (mmHg)	Pb_{CO_2} (mmHg)	pHb	Pa_{CO_2} (mmHg)
−30	66.5 ± 2.7	7.03 ± 0.03	35.3 ± 2.1	64.7 ± 1.4	7.02 ± 0.02	34.9 ± 0.2
0	66.8 ± 2.6	7.03 ± 0.03	35.2 ± 2.2	65.3 ± 1.6	7.02 ± 0.03	35.1 ± 0.1
5	77.8 ± 3.5	7.00 ± 0.04	35.8 ± 2.9	78.5 ± 2.4	6.97 ± 0.04	56.4 ± 1.7
10	87.4 ± 5.1	6.97 ± 0.04	30.7 ± 2.2	89.9 ± 2.9	6.93 ± 0.03	60.4 ± 0.3
15	90.6 ± 4.9	6.95 ± 0.03	30.0 ± 2.2	90.4 ± 3.1	6.94 ± 0.03	60.1 ± 0.3
20	91.9 ± 5.2	6.94 ± 0.03	29.5 ± 2.0	91.8 ± 2.9	6.94 ± 0.04	60.2 ± 0.2
25	92.1 ± 4.9	6.92 ± 0.02	29.9 ± 1.8	92.2 ± 2.7	6.95 ± 0.03	60.3 ± 0.3
30	91.7 ± 4.7	6.91 ± 0.02	30.1 ± 2.1	92.7 ± 2.7	6.95 ± 0.03	60.5 ± 0.3
40	91.7 ± 4.6	6.88 ± 0.03	31.3 ± 2.0	93.4 ± 2.6	6.97 ± 0.03	60.3 ± 0.2
50	91.4 ± 4.5	6.86 ± 0.04	34.3 ± 1.9	93.9 ± 2.6	6.97 ± 0.03	60.2 ± 0.2
60	92.0 ± 4.5	6.84 ± 0.04	34.7 ± 1.9	93.9 ± 2.8	6.97 ± 0.03	60.4 ± 0.3
p	0.0001	0.0001	0.0001	0.009	0.0001	
Fisher	0/5–60	0/15–60	0/10–40	0/5–60	0/5–60, 10/40–60	

Values are means ± SE. Pa_{CO_2} and Pb_{CO_2}: arterial and brain tissue P_{CO_2}, pHb: brain tissue pH. Time 0 min indicates acetazolamide (20 mg/kg, i.v.) administration and reducing respiration. p and Fisher values were determined by analysis of variance.
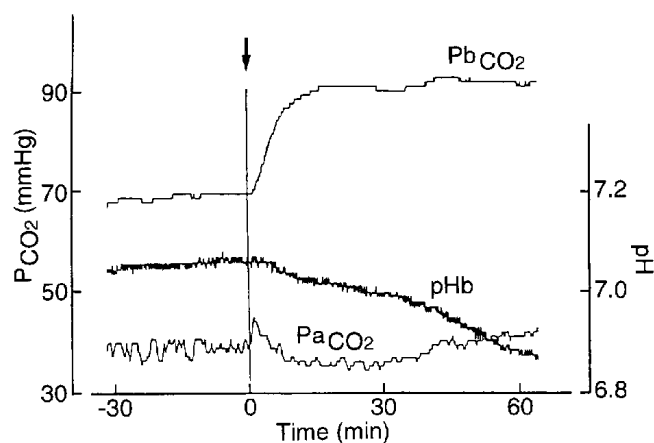

Fig. 1 Representative Pa_{CO_2}, Pb_{CO_2}, and pHb changes in a Group 1 cat. *Arrow* indicates the time of intravenous administration of 20 mg/kg of acetazolamide.
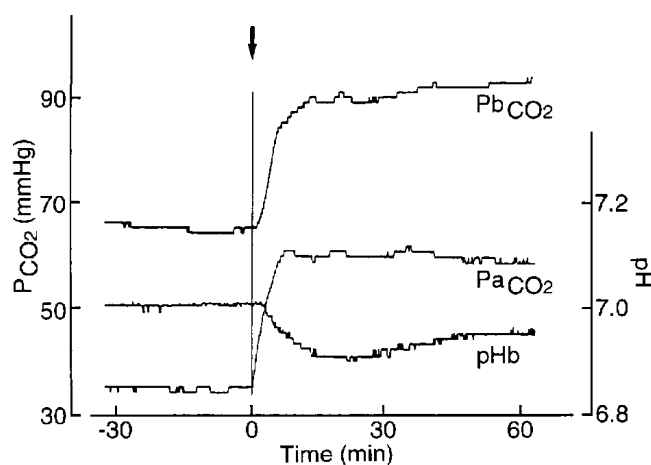

Fig. 2 Representative Pa_{CO_2}, Pb_{CO_2}, and pHb changes in a Group 2 cat. *Arrow* indicates the time at which hypercapnia was induced.

drug infusion. The fall in Pa_{CO_2} was maintained from 10 to 40 minutes. After this plateau phase, Pa_{CO_2} increased gradually and reached a new steady-state value, which was not statistically different from the control value. No significant changes were found in respiratory and heart rates at any point.

Figure 2 shows representative tracings for Pa_{CO_2}, Pb_{CO_2}, and pHb in a Group 2 animal. The Pa_{CO_2} was maintained at 35 ± 1 mmHg to match the Pb_{CO_2} to the control Pb_{CO_2} values in Group 1. Pa_{CO_2} was increased by hyperventilation sufficient to increase Pb_{CO_2} by 25 mmHg, i.e., the increase caused by

acetazolamide administration. pHb decreased from the baseline to the lowest value of 6.93 pH after 10-minute exposure to hypercapnia, and thereafter showed a significant rise from 40 minutes (p < 0.05). Heart rate decreased transiently after changing the ventilation and soon returned to the baseline.

The baseline values in Pb_{CO_2} and pHb in the two groups were not significantly different. Reduction in the rate and depth of respiration changed Pb_{CO_2} values similarly to those of the acetazolamide-treated animals. However, the time courses of pHb
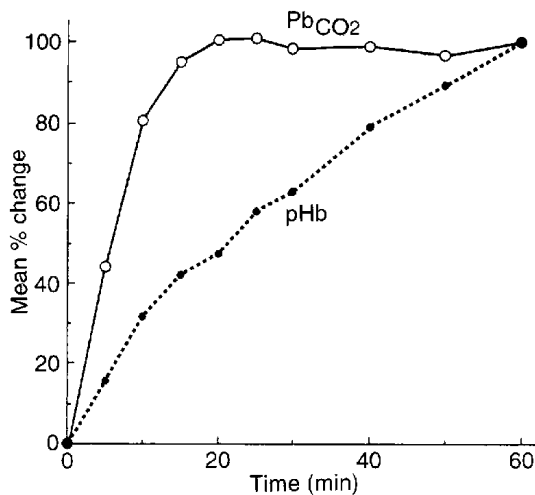
Fig. 3 Mean percentage changes in Pb_{CO_2} and pHb
after intravenous 20 mg/kg acetazolamide
administration.

changes in the two groups were quite different.

Discussion

This study found differences in both the trend and
the magnitude of brain acidosis due to treatment
with acetazolamide and hypercapnia despite main-
tenance of Pb_{CO_2} at similar levels.

The time course of the mean percentage changes
in Pb_{CO_2} and pHb were quite different in animals
treated with acetazolamide (Fig. 3), although the
response time of the CO_2 sensor is slower than that
of the pH sensor. This finding is in contrast to previ-
ous observations of the same mean percentage
changes in P_{CO_2} and pH at the medullary surface.[28]
However, measurement of P_{CO_2} and pH at the brain
surface found a fall in pH persisted whereas P_{CO_2}
was reduced to the control values before treatment
through changes in ventilation.[4] The reaction (CO_2
+ H_2O = H_2CO_3 = H^+ + HCO_3^-) requires 20 sec-
onds to reach 90% change of the total change in plas-
ma.[8] The same time is estimated to be required to
reach equilibrium in brain extracellular fluid be-
cause carbonic anhydrase is not present there. If
both P_{CO_2} and pH are regulated together by this
equilibrium reaction in brain extracellular fluid,
then such a large difference in the mean percentage
change would not occur even if the hydration reac-
tion of CO_2 is uncatalyzed. Therefore, the previous
and our present findings indicate that both brain H^+
and CO_2 can increase independently in response to
acetazolamide.

The exact mechanisms by which acetazolamide in-
duces a rise in Pb_{CO_2} and brain acidification have not

been clarified. The importance of carbonic anhy-
drase in brain tissue has been emphasized in the rise
in Pb_{CO_2},[4] but carbonic anhydrase inhibition in
RBCs causes both decreased CO_2-carrying capacity
of blood and greater P_{CO_2} gradient between tissue
and blood,[5,21,22,31] because acetazolamide injected in-
travenously penetrates the BBB slowly and may take
several hours before the physiological effect is maxi-
mum.[21,23,29] The overall pattern of carbonic anhy-
drase inhibition by acetazolamide injected in-
travenously is simply due to the greatly increased
gradient of P_{CO_2} from tissue to alveolus.[21] Mem-
brane-associated carbonic anhydrase is widely
present on the luminal surface of endothelial cells of
brain capillaries.[9] This type of carbonic anhydrase
is present in the lungs[32] and is involved in CO_2 exclu-
sion from the lungs.[6] The carbonic anhydrase in
brain capillaries is probably important for CO_2 trans-
port from the brain to blood and inhibition may
cause CO_2 retention in the brain.[9,19] Therefore, there
are at least two sources for the rise in Pb_{CO_2} after
acetazolamide administration: inhibition of carbon-
ic anhydrase located either in RBCs or in brain capil-
lary endothelium.

Brain carbonic acidosis might occur via direct in-
hibition of carbonic anhydrase located in brain tis-
sue, but the slow movement of acetazolamide across
the BBB suggests that the rapid pHb change after
drug administration is not caused by this mechan-
ism. The excess rise in Pb_{CO_2} after acetazolamide ad-
ministration may cause the formation of carbonic
acid in brain tissue.[22,28] According to this hypothe-
sis, pHb responses to both acetazolamide and hyper-
capnia should be similar if the time course of Pb_{CO_2} is
the same. However, our study found the fall in pHb
was progressive after acetazolamide administration,
but transient in hypercapnia.

The pHb response to hypercapnia shows the
phenomenon of pH buffering in brain extracellular
fluid due to carbonic anhydrase in RBCs and brain
tissue. Such brain pH buffering capacity is well
known to be activated under hypercapnia and
hypocapnia.[1,2] Our result that the pHb buffering is
inhibited by acetazolamide administration suggests
that one of the pHb regulating mechanisms is car-
bonic anhydrase-dependent. Brain pH is regulated
mainly by transmembrane ion transport in both the
brain capillary wall and the brain cell mem-
brane.[14,24] Especially, Na^+/H^+ and Cl^-/HCO_3^- ex-
changes are important in brain pH regulation.[3,12,14]
In the cerebrospinal fluid, Na^+/H^+ and Cl^-/HCO_3^-
exchanges may be dependent on carbonic anhy-
drase located in the cells of the choroid plexus and
glia.[15,26] Our result that acetazolamide inhibited pHb
regulation is similar to the observation that in-

traperitoneal acetazolamide interfered with carbonic anhydrase-dependent ion transport in the brain cell membrane.[17] However, we believe that this phenomenon cannot be explained by this site of inhibition because of the slowness of acetazolamide penetration across the BBB. Intra- and extracellular pH changes are interdependent in brain tissue.[13] Thus, the inhibition of intracellular pH regulation might be greatly affected by the extracellular pH change. Although our data support the hypothesis that brain capillary endothelial carbonic anhydrase interferes with pH regulation in brain tissue, how intravenously injected acetazolamide affects the pH regulatory mechanism is not shown.

The pHb responses to acetazolamide and hypercapnia are quite different from each other when the values of Pb_{CO_2} are not significantly different at any point during the measurement. Acetazolamide-induced brain carbonic acidosis is not due to the concomitant rise in brain tissue CO_2 tension.

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Commentary

Kohshi et al. have provided important insight into the mechanism of induction of brain acidosis by acetazolamide. In their well designed and creative set of experiments, these investigators have shown clear differences in the temporal profile and magnitude of brain acidosis due to acetazolamide and hypercapnia. By adjusting for Pb_{CO_2} in the two experimental groups, they have shown that the mechanism for acetazolamide-induced brain acidosis is not simply the result of a rise in brain CO_2 tension induced by the pharmacologic agent.

As with most good experiments, this study answers an important question and also raises some new unanswered questions that require further investigation. The authors' scholarly discussion applies their novel finding to existing hypotheses on mechanisms by which acetazolamide induces a rise in Pb_{CO_2} and brain acidification. The results strongly suggest that brain capillary endothelial carbonic anhydrase interferes with pH regulation in brain tissue. Further work is indicated to determine the precise mechanism by which acetazolamide affects the pH regulatory mechanism.

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Dr. Kohshi and his colleagues report interesting data which disclose striking differences in brain tissue pH responses between acetazolamide administration and hypercapnia. They demonstrate that, when acetazolamide is administered intravenously, the brain tissue pH decreases slowly, whereas the increase in CO_2 tension of the brain tissue reaches its maximum level far more rapidly. In contrast, hypercapnia causes a decrease in pH in parallel with an increase in CO_2 tension within the brain tissue. This difference in immediate responses of the brain tissue pH should be taken into account when cerebrovascular responses are analyzed by these procedures. They also demonstrate that, while the decrease in brain tissue pH during hypercapnia is transient, acetazolamide causes the brain tissue pH to decrease progressively. As mentioned by the authors, the slowly progressive decrease in brain tissue pH caused by acetazolamide may reflect disturbances in the mechanisms of pH regulation. The authors suggest that inhibition of carbonic anhydrase located on the capillary endothelial cells of the brain could play a major role in producing such disturbances of pH regulation within the brain tissue. This is another important factor which should be borne in mind when acetazolamide is used clinically.

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Kohshi et al. have used CO_2 and pH sensors, which facilitate continuous monitoring of brain tissue CO_2 tension (Pb_{CO_2}) and pH (pHb), and studied the effects of acetazolamide and hypercapnia on Pb_{CO_2} and pHb. It is well-known that acetazolamide is a potent cerebrovascular dilatator and it is used to examine cerebrovascular reserve capacity in stroke patients. However, the mechanism by which acetazolamide causes tissue acidosis is not completely understood. The authors demonstrated clear Pa_{CO_2}, Pb_{CO_2}, and pHb changes in acetazolamide and hypercapnia groups. Acetazolamide-treated animals showed progressive and persistent falls in pHb associated with Pb_{CO_2} rise. Hypercapnia animals showed the same Pb_{CO_2} rise as seen in acetazolamide-treated animals, but the fall in pHb was transient. Thus, the pHb responses to acetazolamide and hypercapnia are quite different when the values of Pb_{CO_2} are not significantly different at any point during the measurement. They concluded that acetazolamide-induced brain carbonic acidosis was not due to the concomitant rise in brain tissue CO_2 tension. This conclu-

sion rises another question about the discrepancy between the rapidity of the brain acidosis after acetazolamide administration and the slowness of acetazolamide penetration across the BBB. Further new information about the biochemical effects of acetazolamide on cerebral pH regulation are necessary to answer these complex problems.

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