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The Influence of Hypocarbia on the Resolution of Transient Increases in Brain Extracellular Potassium

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The effect of acute hypocarbia on baseline extracellular K^+ concentration ($[K^+]_e$) and its effect on the ability of the cerebral microenvironment to recover from transient increases in $[K^+]_e$ has been assessed in rats. Spreading depression of cortical activity was used to present a reproducible K^+ load to the extracellular space. Baseline $[K^+]_e$ and the half-time for resolution of the $[K^+]_e$ changes seen with spreading depression waves were measured for the hypocarbic and normocarbic states by means of double-barrelled K^+ microelectrodes placed approximately 400 μm below the cortical surface. Three spreading depression waves were initiated in each animal for the two CO_2 states. In group 1 (n = 10), the rats were initially normocarbic (Pa_{CO_2} 41.6 ± 3.0 mmHg; mean ± SD), then hypocarbic (Pa_{CO_2} 19.0 ± 2.5 mmHg) for the second series of measurements. The baseline $[K^+]_e$ was significantly higher in the normocarbic state 3.4 ± 0.4 *versus* 3.0 ± 0.4 mM l^{-1}, $P < 0.01$ (paired *t* test). During normocarbia, the K^+ load ($\Delta[K^+]_e$) presented to the extracellular space following spreading depression was 49.4 ± 7.5 mM l^{-1}, n = 10 (peak $[K^+]_e$ − baseline $[K^+]_e$). The half-time for resolution of the presented $[K^+]_e$ load was 24.3 ± 6.1 s. Following hypocarbia of 1.4 ± 0.6 h, there was no change in $\Delta[K^+]_e$ (49.0 ± 6.0 mM l^{-1}) but resolution $t_{1/2}$ had increased to 35.8 ± 11.2 s, $P < 0.01$ paired *t* test. For group 2 (n = 10), the opposite experimental sequence was followed with hypocarbia (Pa_{CO_2} 20.8 ± 1.9 mmHg) established for a mean of 1.4 ± 0.3 h prior to recording session 1. Again, the baseline $[K^+]_e$ was higher when the animals were normocarbic 3.3 ± 0.3 *versus* 3.0 ± 0.5 mM l^{-1} during hypocarbia, $P < 0.05$. The half-time for recovery was significantly longer with hypocarbia (33.8 ± 9.3 s) than with subsequent normocarbia (28.8 ± 6.9 s), $P < 0.05$, despite similar $\Delta[K^+]_e$ (54.0 ± 6.4 *versus* 51.6 ± 4.6 mM l^{-1}, respectively). These results demonstrate that, in the non-stressed state, hypocarbia did not induce ischemia at the level of the cerebral microenvironment, as there was no evidence of K^+ efflux. However, when a reproducible K^+_e load was presented to the microenvironment, hypocarbia reversibly increased the time required to clear such a K^+_e load by 20–50%. This increase in half-time for resolution of the presented K^+_e load suggests hypocarbia to a Pa_{CO_2} of 20 mm Hg has a modest and reversible impact on K^+_e clearance compared to experimentally induced stresses, such as ischemia, anoxia, or profound hypoglycemia. (Key words: Brain: cerebral blood flow; spreading depression. Carbon dioxide: hypocarbia. Ion: extracellular potassium.)

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THERE HAVE BEEN few attempts to assess how hypocarbia affects the brain at the level of the microenvironment. Indirect experimental evidence indicates that hyperventilation to a Pa_{CO_2} of 20 mmHg or less results in cerebral tissue hypoxia through decreased cerebral blood flow. Such evidence includes slowing of the EEG,[1] increased cerebrospinal fluid and brain tissue lactate levels,[2] decreased cerebral mixed venous O_2 tensions,[3] and decreased mental acuity in volunteers actively hyperventilating.[4] More direct experimental evidence has demonstrated that brain tissue P_{O_2} decreases with hyperventilation,[5,6] and that tissue P_{O_2} can be increased with hyperoxia.[5] Using available human experimental data, Sorensen has theorized that an identical cerebral $P\dot{v}_{O_2}$ is obtained with normoxemic hypocarbia (Pa_{CO_2} = 20) as with hypoxemic normocarbia (Pa_{O_2} = 20).[7]

It is well established that cerebral ischemia is associated with release of K^+ to the extracellular space when cell membranes fail to maintain normal concentration gradients.[8,9] If hypocarbia results in cerebral ischemia secondary to decreased blood flow, then release of K^+ to the extracellular space would be anticipated. This paper investigates this possibility by assessing the effect of hypocarbia on baseline extracellular K^+ concentration ($[K^+]_e$) during thiopental anesthesia in rats. We have also investigated the impact of hypocarbia on clearance of a K^+ load presented to the extracellular space. The half-time for resolution of induced transient increases in brain $[K^+]_e$ is increased whether related to ischemia,[10] hypoxemia[11] or hypoglycemia.[12,13] In this study, we have used spreading depression waves as the means to transiently, but markedly, increase $[K^+]_e$ to assess how hypocarbia affects the ability of the cerebral microenvironment to clear a potassium load.

Methods

Twenty male hooded rats weighing 240–370 g were initially anesthetized with diethyl ether, then injected with 50 mg · kg^{-1} of thiopental intraperitoneally. Following induction, a tracheostomy was performed, and an arterial catheter was placed in the tail artery for blood pressure measurement and arterial blood gas determinations. At this time, an additional 50 mg · kg^{-1} of thiopental IP and 2 mg of d-tubocurarine IM was administered, and the animal's airway was connected to a small animal ventilator. Throughout all time periods, the Pa_{O_2} was maintained over 100 mmHg by enriching the inspired air with O_2.

The rats received additional anesthetic, 25 $mg \cdot kg^{-1}$ of thiopental IP hourly. To maintain intravascular volume, 1 ml of normal saline was given after each arterial blood gas determination. The animal was placed on a warming pad, and the rectal temperature was monitored and maintained at 36–38° C. The head was fixed in a head holder insulated from ground. A 5 mm craniotomy was performed over the left parietal cortex with a trephine, and the dura turned carefully to expose the underlying cortex. A 1 mm length of 1 cm OD rubber tubing was fixed with cyanoacrylate ester glue to the skull bones so that a small pool of mock CSF could superfuse the cortex. A flask of mock CSF was bubbled with 5% Co_2/95% O_2 to adjust superfusate *p*H to approximately 7.35, then gravity-fed through polyethylene tubing to the cortical surface. The solution was warmed to 36–38° C by flow through a small heat exchanger. The temperature was measured with a mini-thermocouple. The superfusate fluid was removed by siphon adjusted to maintain the brain pool at a 0.5–1.0 mm depth. A spreading depression wave was induced by electropneumatic switching[14] to a solution containing 150 mM KCl for 30 s.

The magnitude and duration of changes in extracellular K^+ concentration ($[K^+]_e$) and the voltage changes (V_e) associated with spreading depression waves were recorded with double-barrelled K^+ liquid ion exchanger microelectrodes placed 400 μm below the cortical surface (fig. 1). The changes in V_e are pathognomonic of a spreading depression wave,[15] and served as confirmation that the $[K^+]_e$ changes were secondary to this event. Three spreading depression waves separated by 8-min intervals were initiated in each recording session. The ionic changes associated with spreading depression have all reverted to baseline within this time frame.[16] After each recording session, the electrode was removed to be recalibrated and then repositioned in the same area of cortex.

In group 1 (10 animals), ventilation was adjusted until Pa_{CO_2} was approximately 40 mmHg. Following the first recording session, by increasing the tidal volume, the animal was hyperventilated for approximately 1.5 h to a Pa_{CO_2} of about 20 mmHg. The second recording session was obtained at this time. In group 2 (10 animals), the opposite experimental sequence was followed with hypocarbia established 1.5 h before the first recording session. Minute ventilation was then decreased to induce normocarbia, which was maintained for 1.5 h prior to the second recording session.

Arterial blood was drawn into heparin-coated glass pipettes (volume 100 μl). The O_2 and CO_2 tensions were measured with Radiometer® P_{O_2} and P_{CO_2} electrodes calibrated before each measurement. Such measurements were made before and after each recording session and at 15-min intervals, until stable, during the change from one Pa_{CO_2} state to another.

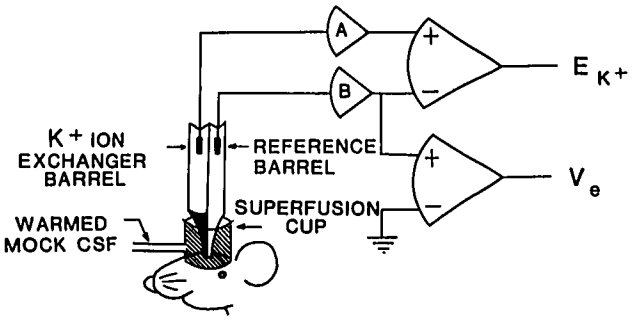

FIG. 1. The experimental set-up: A superfusion cup surrounds the craniotomy site in the parietal cortex. The double-barrelled microelectrode is connected to high input impedance electrometers A and B. The K^+ derived potential (E_{K^+} is the difference between the potential recorded by the K^+ ion exchanger barrel and the potential recorded by the reference barrel (V_e).

MICROELECTRODES AND AMPLIFIERS

The double-barrelled microelectrodes were constructed of theta-capillary borosilicate glass (Clark Electromedical Instruments®) by the method of Lux.[17] The micropipette blanks had a tip diameter of 2–3 μm. The reference barrel was filled with 147 mM NaCl + 3 mM KCl. Corning 477317® K^+ ion exchanger was drawn into the tip of the ion exchanger barrel after the tip was silanized. The back filling solution was 150 mM KCl. The microelectrodes were calibrated in constant ionic strength solutions with $[K^+]$ of 1.5, 3, 6, 12, and 48 mM. They were calibrated before and after each experimental recording session, and, if the K^+ electrochemical potential or reference potential differed by more than 3 mV from the pre-experimental calibration, the measurement was discarded and a new electrode used. The potassium signal and the voltage at the reference barrel (V_e) were recorded directly with high input impedence electrometers. The animal was grounded with a Ag/AgCl wire and a saline bridge into the perfusion cup. The two cortical signals and the blood pressure were displayed and stored on a Nicolet Explorer III digital oscilloscope and a 3-channel chart recorder.

DEFINITIONS AND DATA ANALYSIS

The half-time for recovery of the $[K^+]_e$ increases following spreading depression waves was determined with 500 msec resolution from the oscilloscope records; defined as the time from peak $[K^+]_e$ until 50% return to baseline voltage. The baseline was measured at the onset of the solution change (fig. 2).

The $[K^+]_e$ data was analyzed in the following manner. For each animal, three spreading depression waves were initiated for each CO_2 state. Pooled mean values for baseline, peak $[K^+]_e$, $\Delta[K^+]_e$, and half-time for recovery of

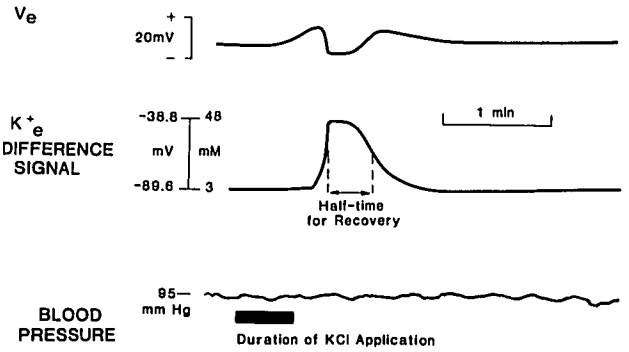

FIG. 2. The data recorded with each spreading depression wave. Spreading depression waves were initiated by application of 150 mM KCl for 30 s (black bar). A double-barrelled K^+ microelectrode was placed about 400 μm below the parietal cortical surface. The top trace shows the potential recorded by the reference barrel of the electrode. A positive, and then a sudden negative, shift in the tissue potential (V_e) herald the ionic changes occurring with a spreading depression wave. The K^+ difference signal shows the prompt extracellular $[K^+]$ changes that occur during spreading depression. Half-time for recovery of the $[K^+]_e$ to baseline was measured as shown (see "Methods").

the $[K^+]_e$ increases were determined for the three spreading depression waves. Within group comparisons of the pooled $[K^+]_e$ data were by Student's *t* test for paired data; $P < 0.05$ was considered significant. Between-group comparisons of pooled data were by analysis of variance with Duncan's test[18] applied *post hoc;* significance level was $P < 0.05$.

For each time period, the lowest mean blood pressure recorded during passage of a spreading depression wave was correlated to the half-time for resolution of the $[K^+]_e$ increase. A relationship between these two parameters was considered significant if the correlation coefficient had a *P* value < 0.05. All results are listed as mean ± SD.

Results

Experimental parameters for the two groups of rats are shown in table 1. For the two groups there was no difference in time to the first spreading depression wave or in duration of experiments. Pa_{O_2} and Pa_{CO_2} were assessed at the beginning and end of each time period, as shown in table 2.

TABLE 1. Experimental Parameters for Groups 1 and 2

Parameter	Group 1 Initial Normocarbia	Group 2 Initial Hypocarbia
Weight (grams)	299 ± 41	287 ± 28
Time to first spreading depression (hr)	1.5 ± 0.3	1.4 ± 0.3
Duration of experiment (hr)	3.3 ± 0.6	3.2 ± 0.6

Mean ± SD; $n = 10$.
No significant difference between groups.

The data in table 3 documents the $[K^+]_e$ dynamics for the two experimental groups. Baseline $[K^+]_e$ was significantly lower during the hypocarbic time periods *versus* the corresponding values during normocarbia, $P < 0.01$. The K^+_e load ($\Delta[K^+]_e$) presented to the extracellular space was the same for all time periods, as were the peak $[K^+]_e$ values recorded. For both groups, the resolution $t_{1/2}$ of the K^+_e load presented to the extracellular space was prolonged when the animals were hypocarbic.

In group 1, comparing resolution half-time for time period 1 and 2 revealed a 47% increase in recovery duration associated with hypocarbia of 1.4 ± 0.2 h, $P < 0.01$. In group 2, the initial CO_2 state of the animals was hypocarbia, then normocarbia for time 2. The reverse findings to those in group 1 are demonstrated, with more rapid resolution of the presented K^+_e load when the animals were returned to the normocarbic state, 33.8 ± 9.9 s *versus* 28.8 ± 7.5 s, respectively ($P < 0.05$). Between group comparisons of time period 1 reveals that the normocarbic state was associated with a more rapid clearance of the $[K^+]_e$ load, $P < 0.05$.

The lowest mean blood pressure during recovery from a spreading depression wave was recorded for all waves in each time period. No significant decrease in blood pressure was seen across the group 1 data. However, a significant decrease in blood pressure occurred for the latter time period (normocarbia) in group 2 when compared to time period 1, $P < 0.01$. No intergroup differences in mean blood pressure were noted when comparing corresponding time periods. An inverse correlation between mean blood pressure and resolution half-time was seen in three of four time periods.

Discussion

In this study, we have demonstrated that hypocarbia to a Pa_{CO_2} of 20 mmHg for 1.5 h resulted in lower baseline $[K^+]_e$ than in the normocarbic state. In addition, hypocarbia reversibly prolonged the time required for the cerebral microenvironment to clear an extracellular potassium load. Spreading depression waves were used as the means to increase the cortical $[K^+]_e$, since such waves are easily initiated in experimental animals, and a large and reproducible local K^+_e load of approximately 50 mM l^{-1} is presented to the extracellular space.

For both groups of experimental animals, the baseline $[K^+]_e$ was significantly lower during the hypocarbic state. Hypocarbia is associated with other ion fluxes, particularly with changes in extracellular HCO_3^- and Cl^- concentrations.[19] The decrease in $[K^+]_e$ suggests some membrane influx during hypocarbia. Of more importance is the finding that basal $[K^+]_e$ did not increase with hypocarbia,

TABLE 2. Blood Gas Tensions for Groups 1 and 2

	Group 1 Initial Normocarbia		Group 2 Initial Hypocarbia	
Gas tensions during spreading depression	Time 1 Normocarbic	Time 2 Hypocarbic	Time 1 Hypocarbic	Time 2 Normocarbic
Pa_{O_2} pre	129.2 ± 16.0	153.7 ± 33.5	146.6 ± 31.7	139.5 ± 33.4
Pa_{O_2} post	167.2 ± 38.9*	147.0 ± 29.7	155.2 ± 28.1	160.5 ± 34.6
Pa_{CO_2} pre	41.6 ± 3.0	19.0 ± 2.5†	20.8 ± 1.9	42.1 ± 4.7†
Pa_{CO_2} post	40.9 ± 3.5	19.1 ± 2.5†	19.2 ± 2.3	43.5 ± 4.2†

Mean ± SD; n = 10.
* $P < 0.05$ pre *vs.* post results within time periods.
† $P < 0.01$ within groups *vs.* time 1.

indicating that, despite decreased CBF, substrate delivery was adequate to prevent efflux of K^+ into the extracellular space. There is thus no evidence to suggest ischemia of the cerebral microenvironment at a Pa_{CO_2} of 20 mmHg during basal conditions in these experiments where rats were anesthetized with thiopental.

The other principle consideration in these experiments was an investigation of how hypocarbia affected clearance of K^+_e when $[K^+]_e$ was transiently increased, *i.e.*, a period of intense metabolic stress to the brain. We have demonstrated that hypocarbia is associated with a 20–50% increase in resolution half-times for clearance of a K^+_e load. Since the experimental duration was the same for the two groups and the order of initiating normocarbia and hypocarbia was reversed in group 2, the confounding variables of time and prep deterioration were eliminated when making intergroup comparisons. The peak $[K^+]_e$ and K^+_e load ($\Delta[K^+]_e$) presented to the extracellular space was similar for all time periods, regardless of CO_2 state, despite a lower baseline $[K^+]_e$ during hypocarbia, $P < 0.01$. The $\Delta[K^+]_e$ was more than two orders of magnitude greater than the difference in baseline $[K^+]_e$, suggesting that this baseline difference was of limited consequence when assessing resolution half-times. Since the $\Delta[K^+]_e$ was identical for the two CO_2 states, the 20–50% increase in resolution half-times to clear the K^+_e loads with hypocarbia must be a reflection of delayed K^+_e clearance. Hypocarbia could conceivably affect any of the four routes available for clearance of the K^+_e loads; diffusion away from the site, efflux into the cerebral circulation, entry into glial cells with resultant "spatial buffering," or active uptake of K^+ by neurons.

Diffusion has been demonstrated to have little impact on local clearance of $[K^+]_e$ accumulations in brain.[14,20] Despite a 100% increase in CBF seen at the spreading depression wavefront, efflux of the local K^+_e load into the cerebral circulation is unlikely, as the blood brain barrier is essentially impermeable to K^+.[21] Hansen et al have shown that there is no increase in $[K^+]$ in the saggital sinus following a spreading depression wave in the rat.[21] During passage of a spreading depression wave, there are glial cell-mediated alterations in local $[K^+]_e$ *via* the "spatial buffer" mechanism.[20,22] The effect of alkalinization, induced by decreased CO_2 tensions, on glial cell membrane clearance of K^+_e loads has not been delineated. The remaining mechanism for K^+_e clearance is ATP-dependent ion pumping by neurons.

Substrate supplies necessary for ATP-dependent ion pumping could be diminished during hypocarbia from decreased O_2, or glucose delivery, or both secondary to decreased cerebral blood flow. Retained but decreased cerebro-vascular reactivity to CO_2 following spreading

TABLE 3. Extracellular K^+ Dynamics during Spreading Depression

	Group 1 Initial Normocarbia		Group 2 Initial Hypocarbia	
	Time 1	Time 2	Time 1	Time 2
K^+ dynamics during spreading depression	Normocarbic	Hypocarbic	Hypocarbic	Normocarbic
Baseline $[K^+]_e$	3.4 ± 0.4	3.0 ± 0.4*	3.0 ± 0.5	3.3 ± 0.3†
Peak $[K^+]_e$	52.8 ± 7.5	51.9 ± 6.0	57.0 ± 6.4	54.9 ± 4.7
$[K^+]_e$	49.4 ± 7.5	48.9 ± 6.0	54.0 ± 6.4	51.6 ± 4.6
Resolution $t_{1/2}$ from peak $[K^+]_e$	24.3 ± 6.1	35.8 ± 11.2*	33.8 ± 9.3‡	28.8 ± 6.9†
$\overline{BP}$	110.1 ± 14.1	104.7 ± 15.9	115.3 ± 11.0	99.7 ± 9.2*
Correlation between $\overline{BP}$ and resolution $t_{1/2}$	−0.62	−0.75	NS	−0.48

Mean ± SD; n = 10.
* $P < 0.01$ within groups *vs.* time 1.
† $P < 0.05$ within groups *vs.* time 1.
‡ $P < 0.05$ between groups for corresponding time periods.

depression has been demonstrated by Lauritzen.[23] Decreased brain O_2 tensions[5,6] and increased A-$V_{glucose}$ differences[24] have been demonstrated with hypocarbia during steady state, suggesting impaired substrate delivery to brain tissue. The decrease in substrate supply with hypocarbia could exascerbate the supply/demand ratio to the cerebral microenvironment at a time of marked increase in cerebral energy requirements during passage of a spreading depression wave. These increases in substrate supplies are necessary for the K^+-Na^+ pumping required to return the extracellular ionic environment to normal. Despite a greater than 100% increase in cerebral blood flow,[25] oxygen tension decreases markedly during recovery from spreading depression,[26] and glucose consumption is elevated three-fold.[27] Concurrently, there is a six-fold increase in tissue lactate levels,[16] indicating that substrate delivery is considerably stressed even in the normocarbic state.

Previous workers have shown a relationship between the half-time for resolution of $[K^+]_e$ loads and adequate cerebral substrate delivery. Branston's group demonstrated a four-fold increase in half-time for resolution of spontaneous $[K^+]_e$ transients associated with a decrease in cerebral blood flow from 0.7 ml to peri-ischemic flows of 0.2 $ml \cdot gm^{-1} \cdot min^{-1}$.[10] Profound hypoglycemia can result in spontaneous spreading depression waves, which take minutes for resolution of the $[K^+]_e$ increases.[12,13] Similar delayed recovery of $[K^+]_e$ increases have also been seen during periods of anoxia.[11] Although not proven, our data imply that hypocapnia reversibly, but minimally, diminishes cerebral metabolic reserves.

We have also noted a strong inverse correlation between mean blood pressure and the half-time for K^+_e resolution. A similar relationship has been observed by Astrup *et al.*,[28] who noted that lowered mean blood pressure resulted in decreased K^+_e clearance during seizures. These results suggest CBF is pressure-passive during seizures due to vasoparalysis. Pressure-passive flow possibly also exists at the spreading depression wavefront. The relative increase in resolution half-times seen in these experiments for the second recording session may relate to the decrease in mean blood pressure observed.

In conclusion, these results show that hypocarbia is associated with decreased $[K^+]_e$ during basal conditions. This finding indicates that hypocarbia to a Pa_{CO_2} of 20 mmHg during thiopental anesthesia in the rat is not associated with ischemic blood flow to the cerebral microenvironment, as no evidence of K^+ efflux was demonstrated. However, when the microenvironment was stressed by transiently elevating the $[K^+]_e$, hypocarbia slowed clearance of the K^+ load. We were able to make a quantitative assessment that hypocarbia to a Pa_{CO_2} of 20 mmHg slowed resolution of transient increases in brain extracellular potassium by 20–50% compared to the normocarbic state. The clinical significance of this finding, which occurs when the cerebral microenvironment is metabolically stressed, is unknown at this time. We suggest the mechanism for the increase in $t_{1/2}$ for K^+_e clearance is minimal impairment of substrate delivery secondary to baseline decrease in CBF. Of importance is the knowledge that this affect is reversible and of truly modest magnitude compared with other conditions of decreased cerebral substrate supply, such as ischemia, profound hypoglycemia, or anoxia. Based on the findings in this study, we see no reason to dispute the routine use of controlled hyperventilation during neurosurgical procedures.

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