Effects of Oxygen Saturation and PCO_2 on Brain Uptake of Glucose Analogues in Rabbits

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Abstract:
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■ The effect of oxygen saturation and PCO_2 on brain uptake of glucose analogues was studied in rabbits. Using a modified Oldendorf technique, ^{14}C-labeled glucose analogues with a ^3H_2O reference standard were introduced into the cerebral circulation via the common carotid artery, and the radioactivity of the ipsilateral cerebral cortex was counted and expressed in terms of a brain uptake index (BUI).

Severe hypoxia (oxygen saturation $\leq 18\%$) resulted in approximately a 40% decrease in the BUI of 2-deoxy-D-glucose and a 45% decrease in the BUI of 3-0-methyl-D-glucose. Severe hypercapnia ($PCO_2 = 100$ mm Hg) caused a 45% decrease in the BUI of both of these glucose analogues. Hypercapnia superimposed on severe hypoxia had no additional effect. Hypocapnia ($PCO_2 = 15$ mm Hg) increased the BUI of 3-0-methyl-D-glucose by 35% of the control value, and this increase was extremely sensitive to competitive inhibition. When BUI values were plotted against pH rather than PCO_2 for the same experiments, there was a good correlation with the calculated linear regression.

These results are compared with previous findings on pathologically induced changes in brain uptake of glucose analogues, and the possible role of blood flow is considered in detail.

Additional Key Words   hypoxia   hypercapnia   hypocapnia
hyperoxia   glucose analogue transport across blood-brain barrier

Introduction

□ Glucose is the basic cerebral nutrient, and its uptake by means of facilitated transport has been established.[1] Previous studies have shown that both hyperosmotic blood-brain barrier injury and ischemia cause an increase in facilitated transfer of glucose analogues from blood to brain.[2, 3] The objective of this investigation was to evaluate the effect of altered oxygen saturation and carbon dioxide tension on the transport rather than metabolism of the glucose in the brain. Therefore, the non-metabolizable 3-0-methyl-D-glucose[4] and partially metabolizable 2-deoxy-D-glucose,[5] known competitors for the binding side of glucose substrate on the carrier molecule, were chosen for this investigation.[6-8]

Methods

Young adult male and female New Zealand white rabbits weighing between 2.3 and 3.2 kg were used throughout these experiments in groups of three to 12 animals. For at least 12 hours prior to surgery, animals were deprived of their regular food, but not water. Anesthesia was induced with an intraperitoneal injection of 6% sodium pentobarbital (30 mg per kilogram) and maintained with small intravenous supplements of 2% pentobarbital, as required. With the animal in a supine position, the first surgical incision was made in the midline of the neck for the purpose of exposing the trachea, as well as the right common carotid artery for subsequent cannulation. A tracheotomy was then immediately performed and ventilation controlled with a small animal respirator (Harvard Apparatus Co, Millis, Massachusetts). Intravenous tubocurarine (Lilly) was also administered (1.2 mg in 1 cc) to keep each animal in phase with the respirator. A second incision was made in the groin and the femoral artery cannulated in order to monitor blood pressure (Statham pressure gauge; Brush 440 Recorder by Gould, Inc, Cleveland, Ohio) and withdraw arterial samples for blood gas analysis (Instrumentation Laboratory 313 pH/Blood Gas Analyzer). Once the tracheotomy was completed, the experiments consisted of two 15-minute controlled ventilation periods. For the first 15 minutes all animals were respirated to stabilize them in a normal range of blood gas values. By varying the flow rates of gases through a modified Kreiselman resuscitator (Ohio Chemical and Surgical Equipment Co, Madison, Wisconsin) connected to the ventilator, the concentrations of inspired O_2, CO_2 and N_2 were quickly changed to a particular combination, depending upon the desired blood gas levels, or left unchanged in the case of control animals. After ten minutes of this second ventilation period, the arterial blood pressure was again checked and then a second sample withdrawn for blood gas analysis (the PO_2 and PCO_2 were not shown to change significantly after the first ten minutes of a ventila-

TABLE 1

Effect of P_{O_2} on Brain Uptake of ^{14}C 2-Deoxy-D-Glucose

Group	No. of animals	Range of P_{O_2} (mm Hg)	Range of S_AO_2* (%)	Mean P_{CO_2} (mm Hg) ± SE	Mean pH ± SE	Mean arterial BP (mm Hg) ± SE	Mean BUI ± SE†	Significance level compared with control BUI
Hyperoxia	5	357–498	100	35.2 ± 1.7	7.51 ± 0.02	86.0 ± 2.4	70.83 ± 3.43	NS‡
Control	12	71–100	96–99	32.4 ± 1.0	7.52 ± 0.01	89.6 ± 3.1	68.27 ± 1.99	—
Mild-moderate hypoxia	5	33– 55	65–91	29.8 ± 1.9	7.52 ± 0.02	87.0 ± 4.6	65.48 ± 2.99	NS
Severe hypoxia	9	12– 15	13–18	28.8 ± 1.8	7.50 ± 0.01	78.3 ± 4.1	39.40 ± 0.88	P < 0.001

*Arterial oxygen saturation.
†Brain uptake index ± standard error.
‡Not significant.

tion period). In selected experiments (controls, hypoxia, hypercapnia and hypocapnia) a venous blood sample was also withdrawn at this time for the purpose of determining the serum glucose level by a modified glucose oxidase-peroxidase procedure.[9] At 15 minutes 0.6 ml of a double isotope mixture was injected in less than one second into the cerebral circulation via a polyethylene cannula in the right common carotid artery, and the animal was decapitated with a guillotine exactly 15 seconds later.[2, 3, 10] The radioactive mixture contained approximately 3 μCi of ^3H_2O, used as a reference standard, and approximately 6 μCi of ^{14}C-labeled 2-deoxy-D-glucose (54.5 mCi/mM), 3-0-methyl-D-glucose (53.5 mCi/mM) or sucrose (394 mCi/mM) (New England Nuclear Corp, Boston, Massachusetts) in Elliot's B electrolyte solution (Baxter Laboratories, Milton Grove, Illinois). Elliot's B solution also was used to rinse the cannula immediately before and after the isotope injection. In order to study effects of inhibition on 3-0-methyl-D-glucose uptake, some experiments were carried out using varying concentrations of cold (unlabeled) 3-0-methyl-D-glucose (0.1, 0.5, 5, 20 mM) or cold phlorizin (10 mM) in both the isotope mixture and Elliot's B rinse solution. The brain was removed quickly following decapitation and a portion of parietotemporal cortex from each hemisphere separately weighed, solubilized and digested for radioactive counting in a Beckman LS-250 liquid scintillation system. Uptake of the test substance was expressed in terms of a brain uptake index (BUI) and calculated as follows:

$$BUI = \frac{^{14}C \text{ in tissue}/^3H_2O \text{ in tissue}}{^{14}C \text{ injected mixture}/^3H_2O \text{ injected mixture}} \times 100$$

The brain uptake index is the index of unidirectional fractional extraction of test tracers.

Mean arterial blood pressures were obtained by electric integration in the Brush amplifier-recorder. Values for oxygen saturation (S_AO_2) were derived from a rabbit hemoglobin dissociation curve[11] and corrected for variations in pH.

Results

There was a significant decrease in the brain uptake of both glucose analogues in severe hypoxia (tables 1 and 2). The control BUI values for 2-deoxy-D-glucose and 3-0-methyl-D-glucose were 68.27 ± 1.99 SE and 37.35 ± 1.68 SE, respectively, as compared with 39.40 ± 0.88 SE and 19.30 ± 0.66 SE when the P_{O_2} was lowered to 10 to 15 mm Hg (S_AO_2 = 10% to 15%). In mild-moderate hypoxia and hyperoxia, however, there was no significant change in BUI for either 2-deoxy-D-glucose or 3-0-methyl-D-glucose when compared to the controls. Although mean P_{CO_2} and pH were approximately the same for all groups, the mean arterial blood pressures in severe hypoxia were slightly lower in the 2-deoxy-D-glucose experiments (78 mm Hg) and markedly lower in the 3-0-methyl-D-glucose experiments (63 mm Hg). Figure 1, however, shows that despite a wide range of blood pressures from 55 to 95 mm Hg, there was no related variation in BUI values for 2-deoxy-D-glucose.

Increase in arterial P_{CO_2} resulted in a decrease in

TABLE 2

Effect of P_{O_2} on Brain Uptake of ^{14}C 3-0-Methyl-D-Glucose

Group	No. of animals	Range of P_{O_2} (mm Hg)	Range of S_AO_2* (%)	Mean P_{CO_2} (mm Hg) ± SE	Mean pH ± SE	Mean arterial BP (mm Hg) ± SE	Mean BUI ± SE†	Significance level compared with control BUI
Hyperoxia	4	369–494	100	31.0 ± 1.5	7.51 ± 0.03	83.8 ± 1.3	34.96 ± 0.44	NS‡
Control	7	68– 99	95–99	30.1 ± 0.9	7.54 ± 0.01	82.9 ± 4.7	37.35 ± 1.68	—
Mild-moderate hypoxia	3	33– 44	74–88	30.3 ± 1.5	7.59 ± 0.04	80.0 ± 10.4	37.55 ± 2.22	NS
Severe hypoxia	4	10– 12	12–13	27.5 ± 1.0	7.52 ± 0.03	62.5 ± 4.3	19.30 ± 0.66	P < 0.001

*Arterial oxygen saturation.
†Brain uptake index ± standard error.
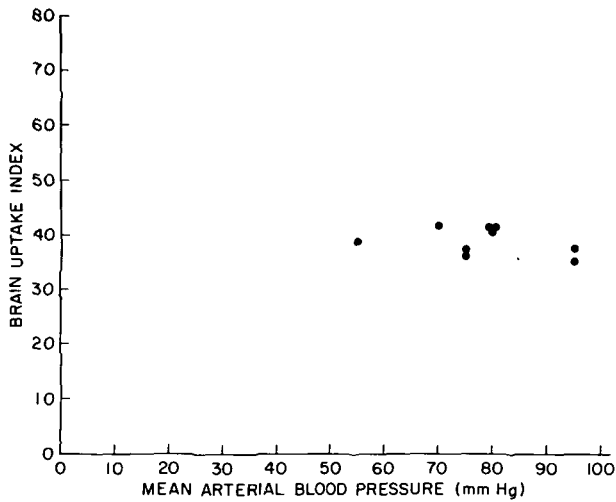‡Not significant.

FIGURE 1

Effect of mean arterial blood pressure on brain uptake of ¹⁴C 2-deoxy-D-glucose in severe hypoxia. These points represent the same nine experiments described in table 1, severe hypoxia group.

BUI for both glucose analogues (fig. 2). The BUI for 2-deoxy-D-glucose decreased to approximately 37 when the P_{CO_2} was increased to 100 mm Hg. If expressed in terms of pH (fig. 3), there was an equivalent fall in BUI with a decrease in pH to 7.10.
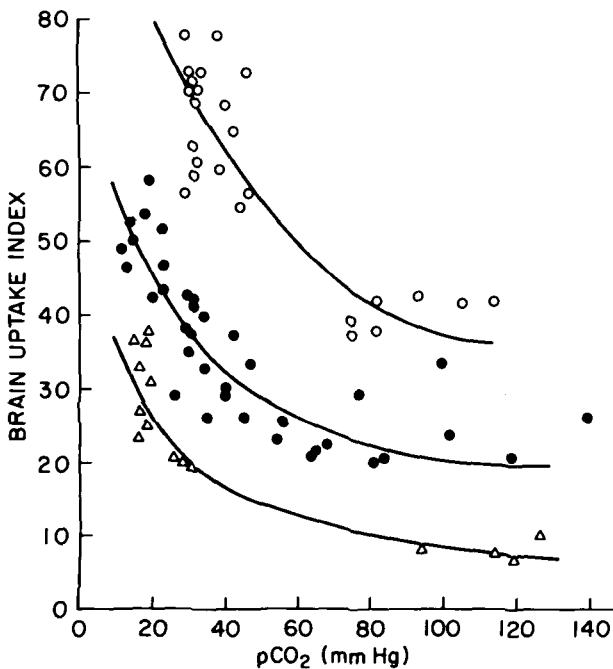

FIGURE 2

Effect of P_{CO_2} on brain uptake of ¹⁴C-glucose analogues. Each point represents a separate experiment. Arterial oxygen saturation was 88% or higher in all experiments, and mean arterial blood pressures were within normal limits. The isotope mixture injected contained either ¹⁴C 2-deoxy-D-glucose (○), ¹⁴C 3-0-methyl-D-glucose (●), or ¹⁴C 3-0-methyl-D-glucose with 10 mM phlorizin (△). Curves are approximated and are not calculated.

Similarly, the BUI for 3-0-methyl-D-glucose decreased to approximately 20 at a P_{CO_2} of 100 mm Hg or a pH of 7.10. When severe hypercapnia was superimposed on severe hypoxia (fig. 4), there was no additional change in the BUI of either glucose analogue. Also, the data in figures 2 and 3 show an increase in the BUI of 3-0-methyl-D-glucose with hypocapnia and resulting respiratory alkalosis: at a P_{CO_2} of 15 mm Hg and a pH of 7.75, the BUI increases to approximately 50. It should be noted that the points in figure 3 for pH versus BUI correlate well with the calculated linear regression, whereas curves could only be approximated for P_{CO_2} versus BUI in figure 2.

Two additional series of experiments were performed using 3-0-methyl-D-glucose. First, 10 mM cold (unlabeled) phlorizin, a competitive inhibitor with 3-0-methyl-D-glucose,[12] was injected with the isotope at various levels of arterial P_{CO_2}. The results, seen in figure 2, show that the BUI of 3-0-methyl-D-glucose with phlorizin plotted against P_{CO_2} forms a curve which runs parallel to and significantly below the curve for the uninhibited analogues. Second, inhibition of 3-0-methyl-D-glucose uptake with varying concentrations of cold 3-0-methyl-D-glucose[7] (self-inhibition) was studied in both hypocapnic and control animals (fig. 5). In the hypocapnic animals the BUI with 0.5 mM inhibitor was 25.01 ± 4.28 SE (n = 5), a decrease of 51% from the noninhibited value of 51.23 ± 2.61 SE (n = 5). In the control animals, however, a comparable decrease (49%) from the noninhibited value of 37.25 ± 1.27 SE (n = 6) was seen not with 0.5 mM but with 5 mM inhibitor, which resulted in a BUI of 19.11 ± 1.35 SE (n = 6). Max-
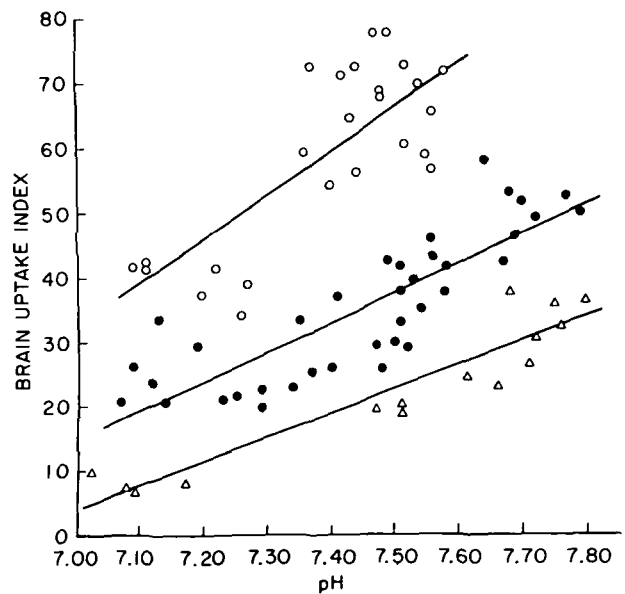

FIGURE 3

Effect of pH on brain uptake of ¹⁴C-glucose analogues. Same experiments and symbols as in figure 2. Lines represent the calculated linear regression for each set of points.
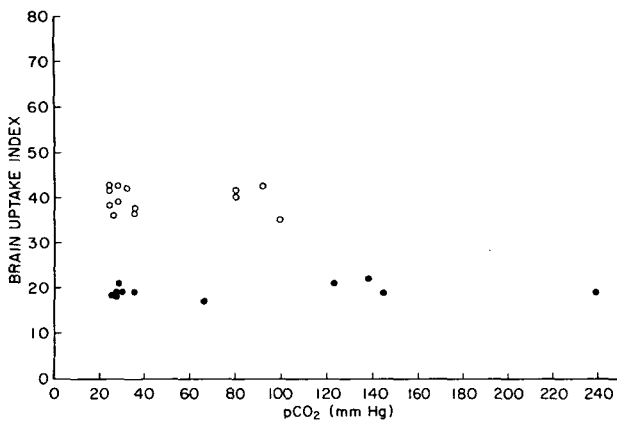
FIGURE 4

Effect of P_{CO_2} on brain uptake of ^{14}C-glucose analogues in severe hypoxia. Oxygen saturation was 18% or less in all experiments. Same symbols as in figures 2 and 3 for experiments without inhibition.

imal inhibition was achieved with 20 mM cold 3-0-methyl-D-glucose, 18.13 ± 2.18 SE (n = 3) for hypocapnic animals and 12.17 ± 2.16 SE (n = 4) for control animals, a decrease of 65% and 67%, respectively, from experiments using no inhibitor.

A comparison of tritiated H_2O uptake with BUI is depicted in figure 6 for 3-0-methyl-D-glucose under various experimental conditions. Within a range of 0.18% to 0.45% ^3H_2O uptake, in which 50% to 75% of animals in each group are found, there is no correlation whatsoever between BUI and water uptake. With higher ^3H_2O uptake, however, all BUI values are low.
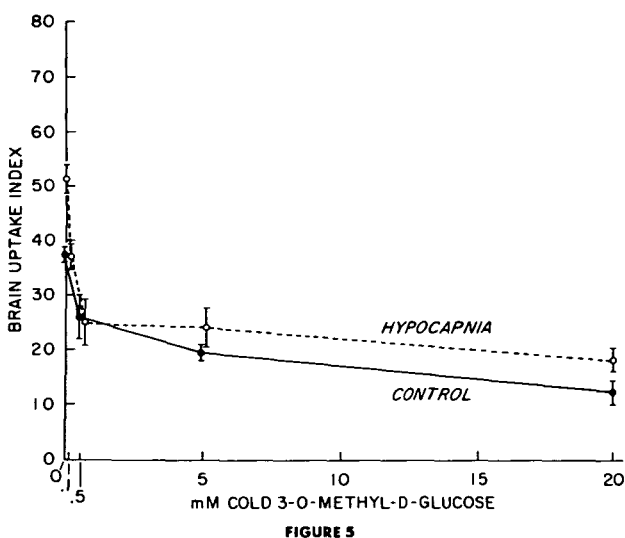
Table 3 shows the results of the effect of P_{CO_2} and P_{O_2} on the uptake of ^{14}C-labeled sucrose with decapitation 15 seconds following injection of the isotope mixture. The control group had a BUI of 4.13 ± 0.12 SE compared with a BUI of 2.68 ± 0.21 SE in severe hypoxia, 2.62 ± 0.36 SE in severe hypoxia with hypercapnia, and 2.15 ± 0.20 SE in severe hypercapnia.

The mean serum glucose (mg %) was 135.7 ± 7.1 SE (n = 7) for controls, 141.8 ± 6.5 SE (n = 9) for hypocapnia, 152.7 ± 21.7 SE (n = 6) for severe hypoxia and 158.2 ± 10.7 SE (n = 5) for severe hypercapnia. None of the experimental values, however, differed significantly from the control value (P > 0.05).

Discussion

The results of this investigation show that lowering the oxygen saturation and/or increasing the carbon dioxide tension in arterial blood can decrease the brain uptake of glucose analogues in the rabbit. The effect on both glucose analogues studied was approximately the same. Severe hypoxia ($S_AO_2 \geq 18\%$) resulted in about a 40% decrease in the BUI of 2-deoxy-D-glucose and a 45% decrease in the BUI of 3-0-methyl-D-glucose. Similarly, severe hypercapnia and respiratory acidosis, with a P_{CO_2} of 100 mm Hg and pH of 7.10, resulted in about a 45% decrease in the BUI of both 2-deoxy-D-glucose and 3-0-methyl-D-glucose
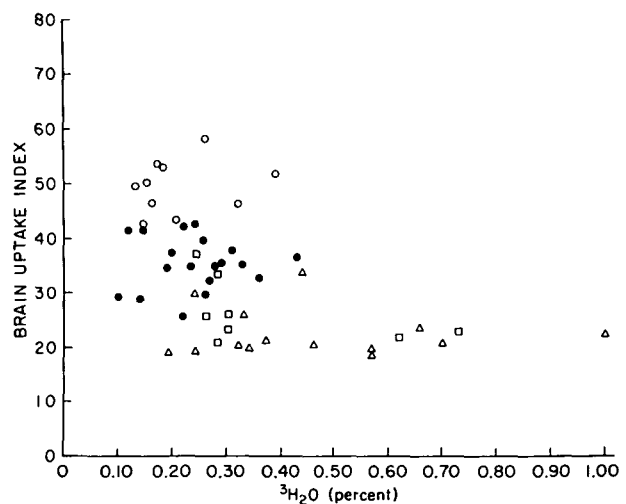

FIGURE 5

Self-inhibition of ^{14}C 3-0-methyl-D-glucose with cold (unlabeled) 3-0-methyl-D-glucose in control and hypocapnic animals. Each point represents the mean BUI for a group of experiments (minimum of three animals), and all groups were comparable with respect to P_{CO_2} and/or pH. Standard errors of the mean are indicated above and below each point.

FIGURE 6

Comparison of ^3H_2O uptake (ratio of injected to recovered water) with BUI in brain uptake of ^{14}C 3-0-methyl-D-glucose under various experimental conditions. Each point represents a separate experiment. Symbols are as follows: (o) hypocapnic — $P_{CO_2} < 25$ mm Hg, $S_AO_2 > 90\%$; (●) hyperoxic, control and moderately hypoxic — S_AO_2 100%, >95% and 74% to 88%, respectively, and all with P_{CO_2} 25 to 40 mm Hg; (□) moderately hypercapnic — P_{CO_2} 41 to 70 mm Hg, $S_AO_2 > 90\%$; (Δ) severely hypercapnic — P_{CO_2} 80 to 140 mm Hg, $S_AO_2 > 85\%$; severely hypercapnic and hypoxic — P_{CO_2} 120 to 240, $S_AO_2 < 16\%$; and severely hypoxic — P_{CO_2} 25 to 40, $S_AO_2 < 15\%$. At least 50% of each group are found between 0.18% and 0.45% ^3H_2O uptake.

694

TABLE 3

Effect of P_{O_2} on Brain Uptake of ^{14}C-Sucrose

Group	No. of animals	Range of P_{O_2} (mm Hg)	Range of S_AO_2* (%)	Mean P_{CO_2} (mm Hg) ± SE	Mean pH ± SE	Mean arterial BP (mm Hg) ± SE	Mean BUI ± SE†	Significance level compared with control BUI
Control	4	76– 89	97–98	30.3 ± 0.6	7.47 ± 0.02	88.8 ± 6.3	4.13 ± 0.12	—
Hypoxia	3	12– 16	17–19	30.3 ± 1.8	7.49 ± 0.06	66.7 ± 6.0	2.68 ± 0.21	P < 0.01
Hypoxia-hypercapnia	3	15– 19	6– 8	128.0 ± 8.5	6.98 ± 0.02	7.33 ± 8.3	2.62 ± 0.36	P < 0.01
Hypercapnia	3	89–111	91–94	107.3 ± 5.2	7.07 ± 0.03	91.7 ± 4.4	2.15 ± 0.20	P < 0.001

*Arterial oxygen saturation.
†Brain uptake index ± standard error.

from control values. A respiratory alkalosis of pH 7.75 induced by a P_{CO_2} of approximately 15 mm Hg increased the BUI of 3-0-methyl-D-glucose by 35%. Inhibition studies on these hypocapnic animals revealed, however, that they were more sensitive to inhibition than control animals; that is, the Km, or concentration of inhibitor (unlabeled 3-0-methyl-D-glucose) necessary to decrease the BUI by 50%[8] was 0.5 mM in hypocapnic animals as compared with 5 mM in control animals.

Neither glucose metabolism nor serum glucose levels can explain the effects of oxygen saturation and P_{CO_2} on brain uptake of glucose analogues. Even though 2-deoxy-D-glucose is partially metabolized[5] and 3-0-methyl-D-glucose is not metabolized,[4] the BUI of each was affected similarly by hypoxia and hypercapnia. Serum glucose did not differ significantly from control levels in either hypocapnia, hypoxia or hypercapnia.

Due to the fact that P_{O_2} and P_{CO_2} have been shown to have a profound effect on cerebral blood flow, a full interpretation of these results would be aided by a knowledge of the changes in blood flow in these rabbits and the effect of such changes on BUI. Although quantitative determinations of blood flow have not as yet been done in rabbits under these experimental conditions, there is sufficient collateral information in our data to support the contention that these changes in BUI can be explained only partially by changes in blood flow. There must be significant changes, therefore, in permeability.

The data on uptake of ^{14}C-labeled sucrose support the conclusion that lowered P_{O_2} and increased P_{CO_2} result in an increase in cerebral blood flow, since sucrose does not cross a functional blood-brain barrier. The significant decrease in the BUI of sucrose under these conditions simply confirms that less intravascular sucrose will be found in the brain if it is cleared more rapidly from the cerebral circulation by increased blood flow. Although brain uptake of tritiated water has been thought to be only flow limited, recent work by Raichle et al.[13] suggests that water uptake is partly diffusion or permeability limited in the brain. Now, if BUI were only a function of blood flow in these experiments, one would expect

the BUI to be a function of ^3H_2O uptake (ratio of injected to recovered ^3H_2O), regardless of the effect of flow on brain permeability of water. When one plots BUI against the uptake of ^3H_2O, however, as was done in figure 6 for 3-0-methyl-D-glucose, one notes that over 62% of animals under various experimental conditions were within a range of ^3H_2O uptake in which there was no correlation whatsoever between BUI and percent of ^3H_2O uptake. In other words, the ratio of injected to recovered water in the experimental brain (in 62% of the rabbits) did not differ significantly from the ratio of injected to recovered water in the controls. Similar observations were made with 2-deoxy-D-glucose. It is clear, though, that a high ^3H_2O uptake (greater than 0.45%) almost always correlated with a low BUI under experimental conditions which were associated with marked increases of blood flow. A decreased BUI but due to both the increased ^3H_2O (^3H_2O brain/injectate) and ^{14}C 3-0-methyl-D-glucose (^{14}C 3-0-methyl-D-glucose brain/injectate) distribution in the regions with increased blood flow was described by Pardridge and Oldendorf[14] recently.

There is further evidence to support the contention that BUI changes do not simply reflect blood flow changes. First, hypercapnia (P_{CO_2} = 100 mm Hg) has been shown in dogs to have a much stronger dilating effect on cerebral vessels than severe hypoxia (S_AO_2 = 20%).[15] Although the O_2 saturations in these rabbit experiments were slightly lower (around 15%), one would still expect a greater blood flow in severe hypercapnia. However, the BUI values for both glucose analogues under these two conditions were essentially the same. Second, hypoxia (S_AO_2 less than 60%) has been shown in dogs to abolish autoregulation and result in a passive pressure-flow relationship.[15] Figure 1 shows, however, that the BUI of 2-deoxy-D-glucose in severe hypoxia is essentially independent of a wide range of arterial blood pressures which, in the absence of autoregulation, would be expected to result in a correspondingly wide range of cerebral blood flow. Finally, single step hyperoxia to levels above 300 mm Hg has been shown to decrease cerebral blood flow by at least 20% in man.[16] In these rabbit experiments there is no significant change in BUI in a similar single step hyperoxia.

The mechanisms by which glucose uptake is reduced by low arterial oxygen saturation and either increased or decreased by arterial P_{CO_2} are not known and require further study. Blood flow determinations need to be made in order to clarify the relationship of flow with the brain uptake of glucose analogues. Also, since glucose is transferred into the brain by facilitated diffusion and is not energy dependent, it would be important to compare these results with the effects of oxygen saturation and carbon dioxide tension on brain uptake of actively transported substances, such as amino acids. Certain essential and non-essential amino acids have been tested, and the results do not always parallel those found with glucose analogues. For example, the BUI of L-leucine is increased rather than decreased by severe hypercapnia, whereas hypocapnia does not appear to affect the BUI of L-alanine and D-leucine.[17] Recently Betz and colleagues reported that, unlike glucose, ten minutes of anoxia had no effect on leucine transport in the brain.[18]

Finally, the demonstration of a decrease in the BUI of glucose analogues in hypoxia and/or hypercapnia in these experiments must be reconciled with the finding that ischemic gerbils show an increase in facilitated diffusion of glucose from blood to brain. It is true that the gerbils were injected with the isotope five minutes after circulation had been re-established to an ischemic hemisphere,[2] and the increase in BUI, therefore, might represent a rebound phenomenon in a postischemic brain. In fact, preliminary experiments on recovery, in which blood gases are returned to normal before the isotope is injected, have suggested an increase in the BUI of 3-0-methyl-D-glucose after severe hypercapnia.[17]

Acknowledgments

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