Hemodynamic and metabolic concomitants of brain swelling and cerebral edema due to experimental cerebral infarction

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Severe cerebral ischemia was produced in 25 baboons by clamping the carotid and vertebral arteries bilaterally for 10 minutes. Cerebral hemodynamics and metabolism were monitored throughout. Cerebral anoxia was less severe in animals in which a marked pressor response occurred due to ischemia of the vasomotor center, and a reversible type of brain swelling was usual. In those with more severe ischemic anoxia, progressive cerebral edema was a pathological entity. Evidence is presented that cerebral edema was caused by loss of autoregulation of cerebral blood flow (CBF) concomitant with hyperemia and an increase of water and chloride content of brain tissue. Cerebral edema began when CBF was reduced during occlusion and progressed for several hours after termination of occlusion. Evidence is adduced that uncoupling of oxidative phosphorylation may be an important concomitant of cerebral edema.

KEY WORDS: brain swelling, cerebral edema, cerebral blood flow, uncoupling, brain displacement, oxygen consumption, oxidative phosphorylation

A good part of the controversy about the pathogenesis of cerebral edema is due to lack of agreement on terminology as well as the grade of edema. Cerebral edema and brain swelling usually occur together but do not have the same meaning and the terms should not be used interchangeably. Significant degrees of brain swelling can occur unaccompanied by cerebral edema, primarily as a consequence of increased cerebral blood volume. As used in this communication, the terms have been arbitrarily assigned the following meanings:

1. "Cerebral edema": increased volume of brain tissue due to increased water content alone.

2. "Brain swelling": an increase in intracranial contents, and hence, intracranial pressure primarily due to increased water content, cerebral blood volume, or cerebrospinal fluid volume.

Pertinent measurements that are feasible during life include cerebral blood volume, intracranial pressure, cerebral displacement, cerebral venous pressure, and cerebrospinal fluid pressure. From a practical point of view in the management of patients, it is important to distinguish between these two concepts. Even if arbitrary, the distinction is important since the durations of increased cerebral blood volume and increased cerebral water content are different, and one condition is fatal while the other is relatively benign.
Cerebral edema is a serious and potentially fatal complication of cerebral infarction. Its disastrous consequences in patients with brain tumor, brain trauma, and certain systemic disorders are well recognized, but the significance of brain edema associated with cerebrovascular disease has received scant attention.2,6

Cerebral edema has been produced by numerous experimental means.2,10,14,20,45 Opinions concerning the etiology of cerebral edema due to hypoxia are conflicting, however, and the terminology is often vague.40 White, et al.,44 and Zaren, et al.,45 reported that systemic hypoxia caused striking increases in brain volume that persisted for as long as 2 hours. Edstrom and Essex,7 however, were unable to provoke brain swelling by systemic anoxia, hypercarbia, hypotension, or cardiac arrest for 2 minutes' duration. Other investigators also failed to produce cerebral edema following asphyxia and hypoxia.28

Plum, et al.,32 produced regional ischemic anoxia in rat brains with simultaneous unilateral carotid ligation and hypoxia. Edema in the ischemic hemispheres was significant compared with that in the nonischemic hemispheres with increased sodium and water content and decreased potassium. Autopsy studies have revealed that brain swelling becomes maximal 3 to 5 days after infarction produced by occlusion of the middle cerebral artery, and in most reported cases was the cause of death.27,38 Sundt and co-workers41 occluded the middle cerebral artery in squirrel monkeys and found that infarction did not occur if flow was restored within the first 2 hours. A delay of several hours in removing the clip, however, led to fatal cerebral edema.

Our present experiments were designed to investigate the etiology of cerebral edema following temporary cerebral ischemia by occluding the carotid and vertebral arteries in their cervical portions. This method was selected in order to avoid injurious systemic effects to organs other than the brain. Intracranial pressure, displacement of brain, cerebral venous pressure, cerebrospinal fluid pressure, cerebral blood flow (CBF), metabolism, and chloride concentrations were all monitored. The relationship of CBF and metabolism to reversible brain swelling and progressive cerebral edema will be presented, and the results from studies of 2,4-dinitrophenol (2,4-DNP) will be compared since it is a known uncoupler of oxidative metabolism.

The relationship of CBF and metabolism to chloride movement, dc potential changes, impairment of autoregulation, vasomotor responsiveness to CO₂ inhalation, and the results obtained by intravenous injection of glycerol in reducing edema will all be discussed in a companion paper.

Materials and Methods
Twenty-five baboons weighing 4 to 10 kg were used. Intravenous pentobarbital was given in doses of 15 mg/kg of body weight. Atropine, 0.2 mg, was injected intramuscularly. The animals were immobilized with gallamine triethiodide (Flaxedil). Respiration was maintained constant with a Harvard respirator. A Kopf stereotaxic apparatus was used as a head holder. Statham transducers were used to monitor blood pressure from the femoral artery, cerebral venous pressure from the anterior sagittal sinus, cerebrospinal fluid pressure from the cisterna magna, and central venous pressure from the superior vena cava. Intracranial pressure was monitored from the subdural space by means of an implanted balloon.

The CBF was measured as cerebral venous outflow by electromagnetic flowmeters placed around both internal jugular veins.26 Cerebral arteriovenous oxygen difference, (A-V)O₂, was measured with a Guyton analyzer.1,26 Arterial and cerebral venous oxygen tension (pO₂), carbon dioxide tension (pCO₂), pH, and plasma chloride content were also measured.23,26

The pO₂ of the cerebral cortex was measured with a membrane-covered oxygen electrode placed lightly on the pial surface of the parietal cortex and sealed into place with dental cement. Cortical dc potentials were monitored from the parietal pial surface with an electrode containing a saline-agar solution referred to an indifferent electrode placed on the frontal bone. The electroencephalogram (EEG) was monitored and recorded simultaneously with the electrocardiogram (EKG). End-tidal CO₂ was monitored also.26

Plasma chloride was monitored with a
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specially constructed silver chloride electrode and a calomel half cell reference which makes contact with the flowing blood. Cortical swelling was measured by displacement of a specially constructed apparatus consisting of a plastic rod and foot plate resting on the brain (Fig. 1). The steel core was wound with wire to form the inner coil of an inductorium. The outer coil of the inductorium was firmly fixed to the skull and an alternating current (6 V, 60 cps) applied to it. The inner coil was surrounded by a plastic plunger with a footpiece which rested lightly on the pial surface of the cortex. The current in the wire in the plunger was amplified and converted into direct current by means of a diode, and then recorded on the polygraph. Linear movement of the plunger was recorded directly as electrical output on the graph. All the burr holes were sealed with dental cement so that the apparatus and the cranial cavity were a closed system.

Both carotid and both vertebral arteries were temporarily occluded for 10 minutes. The animals were sacrificed when it became evident that one of two events had occurred: either progressive cerebral edema had developed or temporary increase of intracranial pressure had reverted to normal. Such an occurrence usually became apparent within 3 hours of temporary ischemia.

After the animals were sacrificed, the brains were weighed and gray and white matter from the frontal lobe analyzed for water content by comparing dry and wet weights. Coronal sections were also made for histologic examination using hematoxylin and eosin (H & E) and Masson's trichrome stain.

Mean CBF and metabolism values were calculated at 1-minute intervals during continuous recordings. Cerebral oxygen consumption (CMRO₂) was calculated as the product of CBF and (A-V)O₂. Calibrations were made before and after each experiment, and the t-test or the paired t-test was used for statistical comparison.

Results

Cerebral Hemodynamics and Metabolism

The animals were divided arbitrarily into two groups: that in which progressive cerebral edema occurred and intracranial pressure exceeded 250 mm H₂O, and that with reversible brain swelling. Such an arbitrary division does not exclude some edema in animals with intracranial pressure of less than 250 mm H₂O. In 13 animals a sustained and progressive increase in intracranial pressure due to cerebral edema occurred following occlusion of the vertebral and carotid arteries for 10 minutes. Reversible brain swelling took place in 10 animals. Occlusion of the vertebral and carotid arteries was maintained for the same interval of time in both groups of animals. Two animals were omitted from the experiment; one aspirated mucous and in one a hematoma developed.

Mean Arterial Blood Pressure (MABP).

MABP increased immediately after occlusion of both carotid and both vertebral arteries in all the baboons (Figs. 2 and 3). This pressor response appeared to be caused by ischemia of the vasomotor center in the brain stem and persisted despite carotid sinus baroreceptor denervation. MABP increased maximally within 22 seconds after the beginning of occlusion, and the elevation persisted throughout the occlusion. The increase in MABP was significantly higher in the group without progressive brain edema (Fig. 2). The rise in MABP apparently improved collateral blood flow.

Cerebral Blood Flow (CBF).

Immediately following occlusion, CBF decreased and often became unmeasurable (Fig. 3).
Metabolic concomitants of brain swelling and edema

Fig. 2. Intracranial pressure and blood pressure during vascular occlusion. The solid line represents the group with progressive cerebral edema and the dotted line the group with reversible swelling. Asterisks indicate statistically significant differences between groups. Time following unclamping of occluded vessels is expressed in minutes.

Nevertheless, in most animals with a good pressor response, blood could be withdrawn from the torcular Herophili, indicating a residual total CBF of circa 10 ml/min (approximately 10% of normal flow values). In the animals with progressive cerebral edema, the decrease in cortical pO2 was greater and the shift in dc potential larger than in the group with reversible brain swelling. CBF increased when the carotid and vertebral arteries were unclamped and flow restored. Twenty minutes after release, the flow rates were higher than during the steady state (reactive hyperemia, luxury perfusion syndrome) (Fig. 4).

Cerebral Oxygen Consumption (CMRO2). CMRO2 decreased in both groups following bilateral occlusion of the carotid and vertebral arteries, accompanied in most instances by loss of all EEG activity or slowing with a gradual increase of amplitude and frequency after removing the clamps from the arteries (Fig. 4, Tables 1 and 2). Approximately 1 hour after the vessels were unclamped, CMRO2 became significantly higher in the group with progressive cerebral edema compared to those with reversible swelling, although some tendency toward the steady state was noted in all animals. EEG abnormalities were most pronounced in the group with cerebral edema. Transient increases in CMRO2 above steady state levels occurred in the majority of animals in the group with progressive brain edema (Fig. 5).

In the animals with progressive cerebral edema, CMRO2 began to decrease when cerebral edema was well established, usually 2 to 3 hours after unclamping the vessels. As judged by the severely abnormal EEG with a concomitant increase in CMRO2, the dissociation of CMRO2 and cerebral function in

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FIG. 3. Continuous recording of parameters of CBF and metabolism in an animal with progressive cerebral edema. BrSw = degree of brain swelling; CBF lj = CBF measured from left internal jugular vein; CBF rj = CBF measured from right internal jugular vein; CVpO₂ = oxygen tension of cerebral venous blood; A-VO₂ = arteriovenous oxygen difference; TrCO₂ = end-tidal CO₂ measured from tracheostomy; BP = arterial blood pressure recorded from the brachial artery.

...the group with progressive cerebral edema raised the possibility of uncoupling of oxidative phosphorylation and energy production which will be considered in the discussion.

Comparison of Changes in Intracranial Pressure (ICP) with Displacement of the Brain.

Swelling of the brain as determined

FIG. 4. Cerebral oxygen consumption (CMRO₂) and cerebral blood flow (CBF) during occlusion, expressed as ml of O₂ per 100 gm of brain per min, were significantly higher in the group with progressive cerebral edema (solid line) than in the one with reversible swelling (broken line) even though the EEG in the former group deteriorated. Cerebral blood flow was greater in the group with cerebral edema than in the one with reversible swelling. CBF became higher in both groups than during the steady state.
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TABLE 1
EEG changes in Group 1 (cerebral edema)
### TABLE 2

**EEG changes in Group 2 (reversible brain swelling)**

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Metabolic concomitants of brain swelling and edema

by cortical displacement in three animals correlated well with changes in intracranial pressure, as measured with a subdural balloon, and sagittal sinus venous pressure (Fig. 6).

Immediately following occlusion of the carotid and vertebral arteries, intracranial pressure decreased and gradually increased thereafter. In the group with progressive cerebral edema, the intracranial pressure increased with a mean of 103 mm H$_2$O immediately after the start of occlusion to 142 mm H$_2$O immediately before release. In the group with reversible brain swelling, the mean intracranial pressure increased from 82 mm H$_2$O at the beginning of occlusion to 103 mm H$_2$O immediately prior to restoration of flow. In both groups, an enormous increase took place in intracranial pressure immediately after release, then returned to normal in the group with reversible swelling. A secondary increase in intracranial pressure occurred in the group with progressive cerebral edema. Since the increase in intracranial pressure correlated with brain displacement and increased cerebrospinal fluid and intracranial pressures, it appeared that water was accumulating in the brain during the period when CBF was reduced to approximately 10% of the steady state values and continued to do so after release of the occlusion.

Cerebral Arteriovenous Oxygen Difference. The (A-V)$_O_2$ differences increased significantly during the interval of occlusion. During the stage of reactive hyperemia, the (A-V)$_O_2$ decreased significantly in both groups and remained decreased thereafter (Fig. 7).

Cerebrovascular Resistance (CVR). Immediately after the cerebral vessels were unclamped, cerebrovascular resistance (CVR) began to decrease to a greater degree in the group with progressive cerebral edema than in the group with reversible brain swelling.
Fig. 6. Intracranial pressure (ICP) measured with a subdural balloon correlated with brain displacement (Br.D) measured with a special device. Solid line represents ICP and dotted line Br.D.

(Fig. 7). This difference between the two groups was attributed to increased cerebral metabolic rate, causing an increase in CBF. Cerebral anoxia also was more severe in the group with progressive cerebral edema, which tends to promote hyperemia.

**Cerebral Perfusion Pressure.** Effective cerebral perfusion pressure was calculated from the equation:

\[
PP = MABP - \frac{(ICP + ICVP)}{2}
\]

where ICVP is the anterior sagittal sinus pressure. When ICVP data were not available, perfusion pressure was calculated as MABP minus intracranial pressure. Cerebral perfusion pressure decreased from 88 to 79 mm Hg in the group with progressive cerebral edema following termination of cerebral ischemia and was significantly lower in this group than in the animals with reversible brain swelling (Fig. 8). Perfusion pressure in the latter group actually increased to 105 mm Hg when ischemia was terminated. **Cerebral Venous Oxygen Tension (CVpO₂).** Cerebral venous pO₂ (CVpO₂) decreased in both groups during occlusion of the carotid and vertebral arteries, followed by a rebound (hyperoxia), reactive hyperemia, or luxury perfusion (Fig. 9). After releasing the vessels, CVpO₂ persisted at high levels in the group with reversible brain swelling, but in the group in which cerebral edema occurred it decreased progressively to a point somewhat below steady-state levels about 2 hours later.
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**FIG. 7.** A-VO₂ decreased in both groups following termination of temporary cerebral ischemia. CVR decreased significantly during the same time interval in both groups. *Solid line* represents group with progressive cerebral edema; *dotted line* is group with reversible swelling.

**FIG. 8.** Cerebral perfusion pressure became significantly lower both during occlusion and after termination in the group with cerebral edema than in the one with reversible brain swelling.
Fig. 9. Cerebral venous \( pO_2 \) decreased significantly during occlusion in both groups, but the difference between the two groups was not significant. Cortical \( pO_2 \) decreased significantly in both groups during occlusion. After termination of occlusion it was still significantly lower than during the steady state in the group with cerebral edema, while in the other group it was significant only during occlusion. Arterial \( pO_2 \) values did not change significantly throughout the experiments compared with steady state values.

Cortical Oxygen Tension. The cortical tissue \( pO_2 \) in the group with progressive cerebral edema decreased during occlusion from the steady state value of 41 to 11 mm Hg, which was significantly lower than the value in the group with reversible brain swelling (Fig. 9), indicating a greater degree of ischemic anoxia in the group with cerebral edema than in the group with brain swelling. Cortical \( pO_2 \) in the group with reversible brain swelling returned to the steady-state level or above after removing the clamps from the vessels. In the animals with progressive cerebral edema, cortical \( pO_2 \) remained reduced.

Arterial Oxygen Tension. The arterial \( pO_2 \) remained constant throughout the experiments (Fig. 9).

Cerebral Venous Carbon Dioxide Tension (CVpCO\(_2\)). Cerebral venous \( pCO_2 \) (CVpCO\(_2\)) increased considerably in both groups during four-vessel occlusion (Fig. 10). The time course for the change in CVpCO\(_2\) correlated with the duration of reactive hyperemia. Immediately after unclamping the vessels, CVpCO\(_2\) increased rapidly, which was attributed to “washout” of accumulated CO\(_2\) from the brain. Ten minutes later CVpCO\(_2\) returned to steady-state levels in both groups.

Arterial and End-Tidal Carbon Dioxide Tensions. Arterial \( pCO_2 \) and end-tidal CO\(_2\) did not change significantly during the experiments (Fig. 10).

Cerebral Venous and Arterial pH. Cerebral venous pH decreased considerably during the period of ischemia due to the accumulation of CO\(_2\), lactic acid, and other me-
Metabolic concomitants of brain swelling and edema

Fig. 10. Cerebral venous pCO₂ was not significantly different between the two groups. The further increase after termination of occlusion indicates "washout." In the group with cerebral edema, the increase was significant at 5 and 10 minutes during occlusion, and at termination it was significant immediately after and at 1, 2, and 3 minutes compared to the steady state. Arterial pCO₂ did not change significantly throughout the experiments, nor was the difference between the two groups significant. Endtidal pCO₂ changes were similar in nature to the values obtained from the arterial blood measurements.

tabolites (Fig. 11). The decrease in cerebral venous pH was insufficient to account for the EEG abnormalities.

Arterial pH gradually decreased in both groups after cerebral ischemia was induced. The change became statistically significant 60 minutes after restoration of flow.

Central Venous Pressure (CVP). Central venous pressure measured in three animals did not change during the development of cerebral edema.

Correlation of EEG Activity with Cerebral Edema. Sustained, progressive cerebral edema developed in all animals in which the EEG became isoelectric within 2 minutes of occlusion, and EEG activity remained grossly abnormal for 10 to 60 minutes following restoration of blood flow (Table 1). The EEG did not become isoelectric within the first 2 minutes of occlusion in the group with reversible brain swelling, and activity rapidly returned within 10 minutes when the cerebral circulation was restored, even though the frequency and amplitude decreased during ischemia (Table 2).

Intracarotid Injection of 2,4-DNP. Progressive cerebral edema developed in seven animals treated with 2,4-DNP, and CMRO₂ increased well above the steady-state level with a flat EEG. Increased CMRO₂ in these experiments was interpreted as the result of uncoupling of oxidative phosphorylation, which in turn triggered cerebral edema.

Autopsy Findings. At autopsy, in all the animals with progressive cerebral edema, as defined by the physiological parameters measured, the gyri of the swollen brains were widened, the sulci narrowed, and the par-
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Fig. 11. Arterial pH decreased gradually in both groups during ischemia. Cerebral venous pH decreased extensively in both groups also.

enchyma appeared paler and softer in comparison with the brains from the group with reversible brain swelling. Uncal or tonsilar herniations were not observed. In four animals with cerebral edema, the mean water content of the gray matter was found to be 82.5% and that of white matter 71.2% (Table 3). Similar measurements were made in three animals with reversible brain swelling, and the mean value for gray matter was 80.1% and that for white matter 66.2%.

Histological examination revealed poor staining with H & E as well as a spongy appearance and vacuole formation in the white matter of the brains with cerebral edema. Abnormal changes with diffuse, irregular staining compatible with some leakage of plasma proteins through the blood-brain barrier into the tissue were also observed in the edematous brains when Masson's trichrome stain was used. No changes were evident in the nerve cells. These specimens were examined by Garcia and Dodson who, in a series of electron microscopic studies of cerebral infarction in monkeys, showed that edema increased swelling of the smooth muscle cells and the permeability of the astroglial feet around blood vessels to horse-chish peroxidase.
Metabolic concomitants of brain swelling and edema

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* Spongy state and discoloration in the white matter.
† Green staining of white matter with Masson's trichrome stain.
‡ Significant difference between groups.
+++ This animal was excluded from calculation of the means because additional procedures were done at the end of the experiment.
§ Reversible swelling+N₂ inhalation: N₂ inhalation at the end of experiment.
§§ Reversible swelling+asphyxia: asphyxia by slowing of respiration at end of experiment.
** Reversible swelling+cerebral edema: second occlusion with resultant cerebral edema at end of experiment.

**Discussion**

While creation of the two groups was admittedly arbitrary, it was evident that cerebral ischemia and anoxia were greater in the animals in which progressive cerebral edema developed than in those with reversible brain swelling. Electroencephalographic (EEG) and dc potential changes were also more pronounced and persistent in this group. From these experiments, adequacy of the cerebral collateral circulation and the pressor response following induced brain stem ischemia appear to govern the degree of ischemic anoxia and, hence, the possible development of cerebral edema.

This finding is consistent with the earlier study of Lee, et al., who reported that, in the monkey, the EEG was stable during brief...
occlusion of the carotid and vertebral arteries provided the pressor response exceeded 170 mm Hg. The importance of the collateral circulation in maintaining normal EEG was confirmed in one monkey in which all arteries of the neck were ligated prior to occlusion of the carotid and vertebral arteries. In this animal, cerebral ischemia was extremely severe, and the EEG rapidly became isoelectric and remained so following restoration of CBF. On the other hand, hypertension following severe brain injury is known to intensify brain swelling since the cerebral vessels lose their autoregulatory capacity. Evidence of brain stem injury was present in the animals in which cerebral edema developed. Spontaneous, irregular fluctuations in blood pressure are known to occur during anesthesia and have been shown to be due to intermittent activity arising from the brain stem vasomotor center. Paralysis of the vasomotor center with loss of fluctuations of blood pressure was regularly observed in the animals with progressive brain edema but not in those with reversible brain swelling. This finding correlated with the onset of severely abnormal, diffuse changes in EEG activity of apparent brain stem derivation.

Although arterial pCO$_2$ did not change, CVP CO$_2$, increased significantly in both groups of animals during cerebral ischemia and for a short period thereafter. Vasodilatation during both these intervals was partially attributable to increased brain tissue pCO$_2$. The high CBF in the group with cerebral edema could not be accounted for by the increase in calculated tissue pCO$_2$ alone and, therefore, was attributed to vasodilatation caused by other factors such as accumulation of acid metabolites and vascular damage with vasoparalysis.

Reactive hyperemia in the group with reversible brain swelling usually subsided within 10 minutes when accumulated CO$_2$ and acid metabolites had been removed. In contrast, the increase in CBF persisted much longer in the group with progressive cerebral edema associated with a low cortical pO$_2$, which indicated that the CMRO$_2$ had increased or an arteriovenous shunt had developed. No evidence for the latter was found.

Hirsch and Müller, in histological studies, showed patchy areas of ischemic damage to the blood vessels which were compatible with sludging or persistent focal stasis of blood in these areas. Sundt, et al., reported a considerable increase in the number of small cortical vessels with marked dilatation of the microvasculature following middle cerebral artery occlusion. Ames, et al., and Chiang, et al., reported areas of capillary obstruction involving as much as 95% of the surface area following temporary cerebral ischemia in rabbits which they attributed to swelling of perivascular glial and endothelial cells. Cantu, et al., reported reversibility of these effects within 15 minutes to 2 hours after restoration of blood flow. The delay of many minutes before the CBF began to increase was also compatible with resolution of patchy capillary obstruction. In the present study, however, since the blood pressure was greatly elevated following unclamping of the carotid and vertebral arteries, resolution of capillary obstruction was probably more rapid than it might have been had the blood pressure not been elevated. Hossman and Sato have shown that hypertension minimizes the "no-reflow" phenomenon.

Van Harreveld and Tachibana reported an increase in water content and chloride levels of nerve cells, particularly in the apical dendrites, following temporary ischemia. In our experiments, an initial marked increase in intracranial pressure with cerebral edema was observed in all the animals except two.

Intracranial pressure returned to normal in the group with reversible brain swelling, suggesting a reversible decrease in water content and recovery from reactive hyperemia, but intracranial pressure remained elevated in the animals with progressive cerebral edema. In the latter group, the increase in intracranial pressure was caused by several factors. First, autoregulation was impaired, causing an increase in CBF and blood volume which persisted after retained CO$_2$ and acid metabolites had been removed from the brain. Second, the increase in intracranial pressure persisted, apparently due to a gradual accumulation of water in the brain tissue. The increased water content in the parenchyma of the brain progressively compressed the cerebrovascular bed and eventually caused a reduction in CBF, as noted in one animal in which intracranial pressure was monitored for many hours. In our experiments, the water content of the brain was greatest in the group with progressive
Metabolic concomitants of brain swelling and edema

cerebral edema, although it was probably increased above normal in both groups.

Progressive systemic acidosis may follow severe cerebral ischemia, as occurred in the present experiments. This condition was not due to the anesthesia, surgical trauma, or prolonged artificial respiration since seven animals observed for 1 hour during the steady state did not exhibit a tendency to develop systemic acidosis.

Normally, CMRO₂ is closely linked to the formation of ATP. Respiration in cerebral tissue is limited by the rate of phosphorylation and, hence, to reactions yielding phosphate and phosphate acceptors (Fig. 12).²⁵ CMRO₂ increases when uncoupling occurs since the limiting factor is removed.¹⁸,²⁵ Although the uncoupling effect has been considered from in vitro studies as possibly being the triggering mechanism in cerebral swelling, in vivo confirmation has been rare.⁴,²⁰,²¹,²⁵

Cytochrome oxidase activity is reportedly increased by about 25% to 50% in mitochondria isolated from ischemic and hypoxic rabbits.⁸⁹ Hypoxia induced in isolated nerve cells caused increases in both CMRO₂, CO₂ production, and cytochrome oxidase activity.¹² Jilek¹⁹ reported significant increases in CMRO₂ in slices of rat brains after ligature of the carotid arteries prior to sacrifice. German, et al.,⁹ confirmed this finding in dogs, and observed that increased CMRO₂ of 42% was accompanied by an 86% increase in CBF 1½ to 3 hours after cerebral trauma.

Infusion of 2,4-DNP had less uncoupling effect on edematous brain tissue than normal tissue, suggesting that edematous tissue is already partially uncoupled.³⁰ Furthermore, cerebral edema can be blocked if ATP is added to the 2,4-DNP injected into the carotid artery.³⁴

In our experiments, there was apparent dissociation of increased CMRO₂ and decreased cerebral function as judged from the EEG. This dissociation of oxidative metabolism from energy production was associated with progressive cerebral edema and appeared similar if not identical to progressive cerebral edema caused by intracarotid infusion of 2, 4-DNP which is known to be associated with uncoupling of oxidative phosphorylation.

Acknowledgments

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