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The Vulnerability of Gerbils to Focal Cerebral Ischemia

Neurological Signs and Regional Biochemical Changes after Ischemia and Recirculation*

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Summary. Gerbils of both sexes were used to study the effects of 30-min ischemia and subsequent recirculation for 4 and 8 days. The mortality rate was 9% during ischemia and 34% in the recirculation period. No close correlation was found between the extent of metabolic changes and the severity of clinical signs after ischemia. Gerbils exhibited severe clinical signs with metabolic patterns of severe hypoxic damage, but with only slight biochemical changes as well, stressing the necessity of detailed examination in regional metabolic studies. According to planimetrical evaluation the most sensitive indicator of ischemic damage was alteration in pH. Decrease in pH without changes in ATP and NADH was associated with severe clinical signs. Biochemical changes were demonstrated after recirculation in some gerbils having severe clinical signs at the end of the ischemic period. The changes in pH and potassium found 8 days after the ischemic insult stress that a 30-min focal ischemia might have long lasting, perhaps irreversible consequences.

Key words: Gerbils – Focal cerebral ischemia – Recirculation – Mortality – Brain metabolism

Introduction

Literature data are contradictory about the consequences of transient cerebral ischemia. Nearly total biochemical restitution was reported after recirculation following a relatively long period of total ischemia in cats and rats (Hossmann and Kleihues 1973; Nordström et al. 1978), while others reported detectable cell damage in rats even after 2 min of ischemia followed by 7 days of recirculation (Smith et al. 1984).

Focal ischemia has also been studied in various animal models (Molinari 1986). Since the observation of Levine and Payan (1966) several investigations have been carried out on focal ischemic brain damage using the gerbil model. The combination of common carotid artery ligation with occlusion of the external carotid artery on the contralateral side resulted in an increase in the number of animals showing signs of focal ischemia to over 60% (Bosma et al. 1981). Using this model Paschen et al. (1983) found strict correlation between the severity of clinical signs and the extent of regional metabolic changes following 90 min of ischemia.

In the present study the clinical and biochemical consequences of a 30-min focal cerebral ischemia was studied in gerbils. Correlation between the severity of clinical signs and the extent of biochemical changes was also studied, and biochemical changes were investigated 4 and 8 days after recirculation.

Methods

Gerbils (*Meriones unguiculatus*) of both sexes weighing 50–70 g were anesthetized using 1.5%–2% halothane in a mixture of 30% O_2 and 70% N_2. The temperature of the animals was adjusted to 37°C by means of a feed back-controlled heating system. After a midline incision in the neck the left common

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and the rigth external carotid arteries were exposed, cleaned from the surrounding tissue, then clamped by Yasargil clips (Type FD-680, closing force: 0.98–1.28 N) using an operating microscope (Zeiss, Jena). The animals were left to recover from anesthesia and 30 min after the occlusion their clinical signs were scored according to the following scale: (I) consciousness: awake (0), slackened (1), somnolet-soporous (2), comatose (3), (II) spontaneous movements: normal (0), slight clumsiness (1), ptosis, slight paresis (2), jumping and rolling, severe palsy (3), and (III) reaction to pain stimulus: prompt reaction (0), a bit slackened (1), hardly reacts (2), no reaction (3). The severity of clinical signs was characterized in each gerbil by the sum of the points given according to the three standpoints. The clips were removed thereafter and the wound was closed. The common and external carotid arteries of the 3 control gerbils were exposed but not occluded.

The animals were divided into 3 groups: (1) 30-min occlusion without recirculation, (2) 30-min occlusion followed by 4 days of recirculation, and (3) 30-min occlusion followed by 8 days of recirculation.

At the end of the recirculation period the clinical signs and behavior of the animals were scored again, then, after halothane anesthesia, the gerbils were immersed in liquid N_2, where they were stored till further procedures.

Evaluation of Regional Differences. The brains were placed in a cold box at −20°C then cut serially using a cryostat into 20-μm thick coronal sections, starting 1.7 mm in front of the bregma (the crossing point of the coronal and sagittal sutures). Consecutive sections were used for regional determination of the distribution of pH, ATP, and potassium. The next 20 sections were not studied, then adjacent sections were again taken for regional determinations. This method of slicing the brains was continued till the posterior part of the hippocampus was reached according to a stereotaxic gerbil atlas (Loskota et al. 1974). The last section was used for the regional determination of hemoglobin, and from the cut surface of the brain the NADH fluorescence was recorded.

Tissue pH. Regional tissue pH was determined on cryostat sections by the umbelliferone method of Csiba et al. (1983). The sections were incubated at 0°C with umbelliferone, a fluorescent pH indicator, illuminated with 370 nm UV light and the fluorescence was photographed using a 450 nm filter. Quantitative pH analysis was not carried out in this study.

Regional ATP Content. Freeze-dried cryostat sections were prepared for qualitative imaging of ATP content using the bioluminescent technique described by Kogure and Alonso (1978). Specific bioluminescence was evoked in the dark by incubating tissue sections with a solution containing an extract of Firefly lanterns (Sigma, St. Louis, USA) and recorded on photographic film.

Regional Potassium Content. Cryostat sections were treated with sodium cobalt nitrite for imaging of potassium content (Mies and Hossmann 1983). The resulting brown-colored reaction product which is a function of the tissue potassium concentration, was photographed.

Regional NADH Content. The cut surfaces of the brains were illuminated with UV light and NADH fluorescence was recorded according to the method of Ji et al. (1975) with a barrier filter at 450 nm.

Regional Hemoglobin Content. For the determination of regional hemoglobin distribution a special reagent paper was used (courtesy of Boehringer, Mannheim FRG). Cryostat sections were layered on these enzyme- and indicator-soaked strips, and this modfied benzidine reaction resulted in blue color reflecting the hemoglobin (blood) content of the tissue (Kutter 1983).

Statistical Methods. The extent of regional changes was evaluated planimetrically, the areas of changes were given as a percentage of the total hemispherical cut surface area. Regression analysis and the paired *t*-test were carried out for comparison of the regional changes in pH and ATP, and the clinical score to the extent of metabolic changes using a laboratory computer.

Results

30 Minutes of Ischemia Without Recirculation

Carotid occlusion was performed in 54 gerbils, and 5 of them died within 30 min. The brains of 8 gerbils, each having severe clinical signs (score higher than 6) were frozen in situ at the 30th min of ischemia without recirculation. Very surprisingly, no strict correlation was found in them between the severity of clinical signs and the metabolic changes. Figure 1 represents the metabolic findings of the control brain. Figures 2–4 show the different biochemical patterns found after ischemia. Similar clinical signs were associated with very different metabolic patterns.

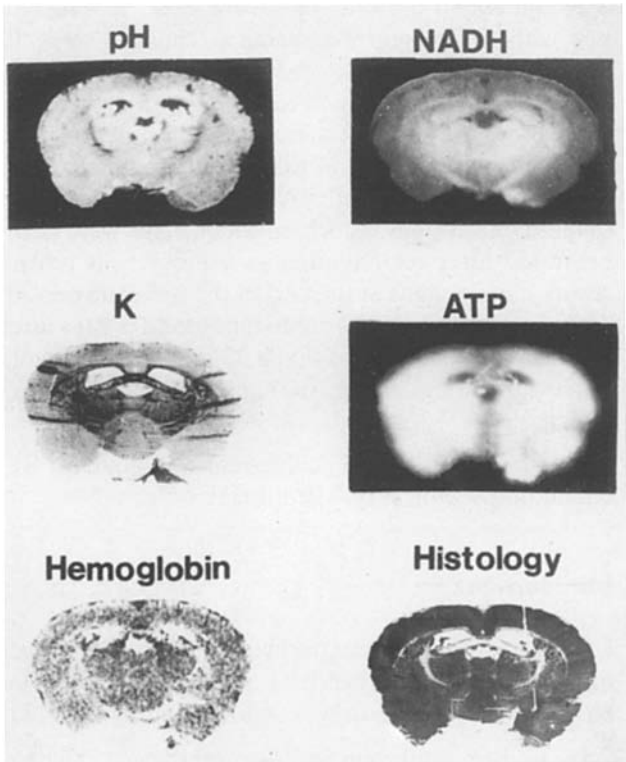

Fig. 1. The metabolic pattern of the control brain. No focal alterations

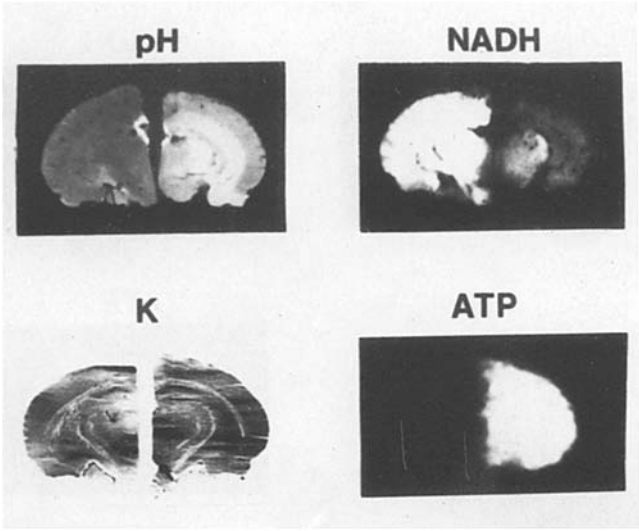

Fig. 2. Metabolic changes after 30 min of ischemia. Acidic pH shift, ATP depletion (*dark areas*), and intensive NADH fluorescence in the whole ischemic hemisphere

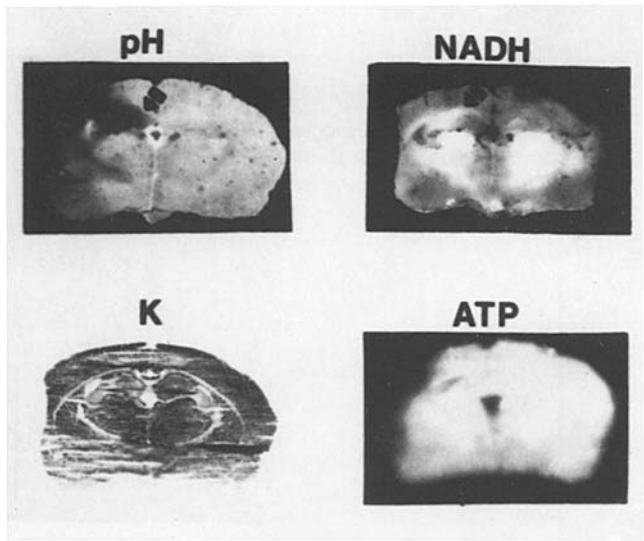

Fig. 3. Metabolic changes after 30 min of ischemia. Normal and decreased ATP bioluminescence in the acidic area, increased NADH fluorescence in the hippocampus of the affected hemisphere (*arrows*) and in the basal ganglia of both sides

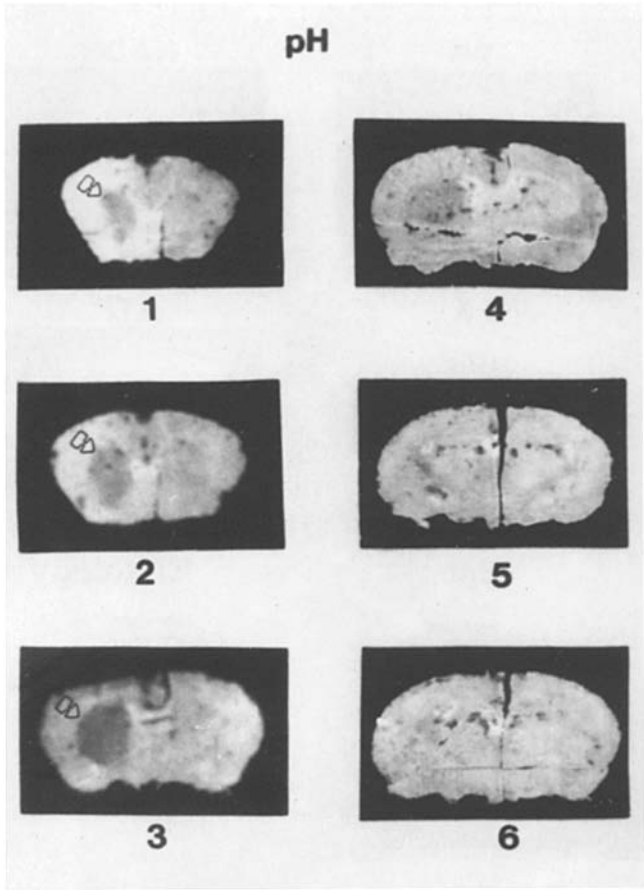

Fig. 4. Metabolic changes after 30 min of ischemia. Acidic area in the frontal part of the affected hemisphere (*arrows*)

Table 1. The mortality of gerbils during ischemia and recirculation

Time of death	During the 30 min of ischemia (n = 54)	During recirculation (n = 41)		
		Within the 1st h	Between 1–24 h	After 24 h
Rate of death	9%	15%	15%	4%

Observations after Recirculation

Recirculation was performed in 41 gerbils, 34% of them dying during the recirculation period. The most critical part of recirculation was the first hour after the removal of the clips: nearly half of the losses occurred in this period (Table 1). At the end of the recirculation period only 3 of the 27 survivors had mild clinical signs (score: 1–3, none of them exhibited regional metabolic differences) while the rest showed complete neurological recovery.

Regional Changes after Recirculation

Though most of the gerbils exhibited complete neurological and biochemical restitution (Fig. 5), despite functional recovery some gerbils presented regional biochemical differences. Despite total functional restitution after severe clinical signs at the end of ischemia, acidic or alkaline pH shift, potassium depletion, and histological damage was observed in the cortex or basal ganglia of the affected hemisphere in a few animals after 4 and 8 days of recirculation (Fig. 6). The areas of ATP depletion are plotted against the areas of regional pH changes in each ger-

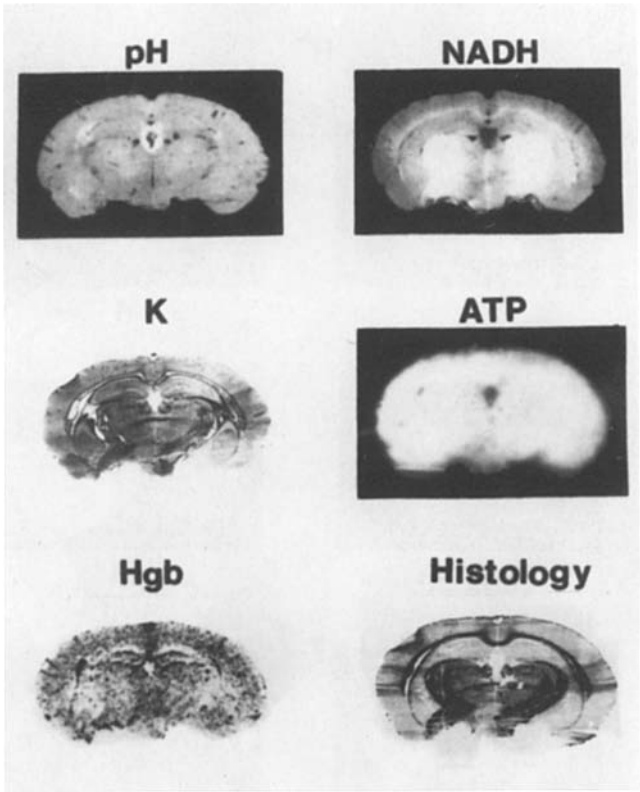

Fig. 5. Ischemia for 30 min followed by 8 days of recirculation. Complete metabolic recovery

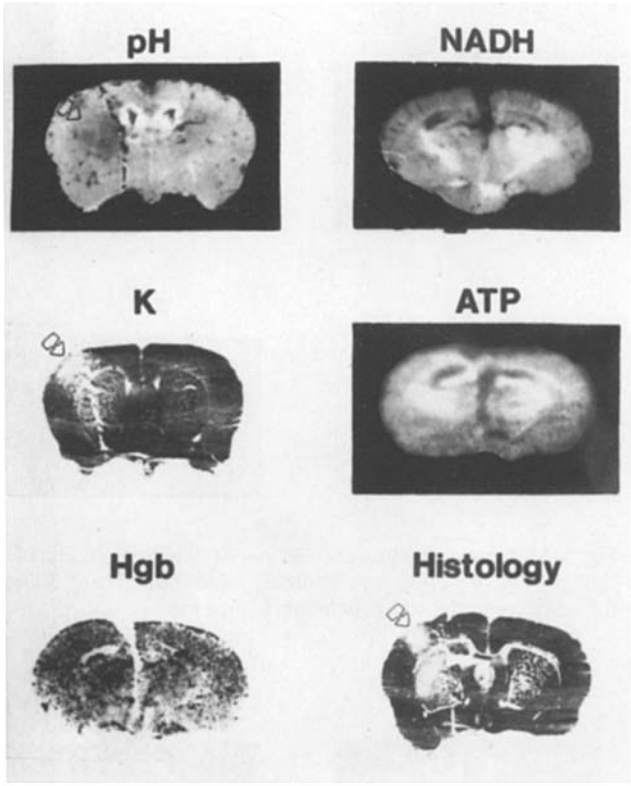

Fig. 6. Ischemia for 30 min followed by 8 days of recirculation. Acidic area, potassium depletion, and histological damage (*arrows*) in the affected hemisphere

bil in Fig. 7. The area of pH alteration was greater than that of ATP depletion.

Correlation Between Signs and Metabolic Changes

The planimetrically evaluated areas of pH changes correlated with the clinical score observed just before freezing of the brain in situ (Fig. 8) after ischemia or recirculation. The figures showed that in general, the higher the score, the more extended the regional pH alteration.

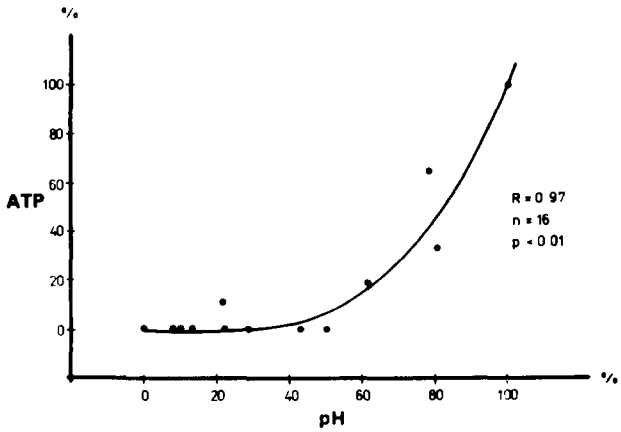

Fig. 7. Correlation between the extension of pH-altered and ATP depleted areas. 100% = total hemispherical cut surface area

Discussion

The vulnerability of gerbils to focal ischemia

Contradictory data have been reported on the rate of gerbils exhibiting signs for focal ischemia following extracranial artery occlusion. Levine and Payan (1966) found that unilateral common carotid artery occlusion resulted in clinical signs in 20% of the gerbils, while this rate was found by others to be 40% (Yanagihara 1978), 60% (Harrison et al. 1973), and less than 20% (Bosma et al. 1981). Modifying the original model by occluding the contralateral external carotid artery as well (Bosma et al. 1981), meant that gerbils with clinical signs were obtained at a relatively constant rate (60%–70%). Using the latter model, however, neither Bosma et al. (1981) nor Paschen et al. (1983) reported the mortality rate.

Using the same model definite clinical signs were found in more than the half of the animals in our experiments, so our gerbil strain seemed to be suscep-

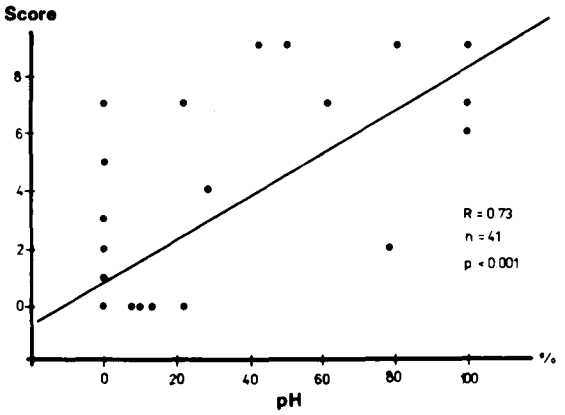

Fig. 8. Correlation between the extension of pH-altered area (in % of total hemispherical cut surface area) and the clinical score at the moment of freezing

tible to this model of ischemia. This sensitivity was also indicated by the relatively high mortality rate during the experiments. The 9% mortality during ischemia was partly due to the operation procedures (mechanical lesion of the vagus nerve) and partly to brain damage. The gerbils that died in the first hour of recirculation (15% of recirculated animals) usually exhibited stridorous breathing then comatose state before death, so in these cases early cerebral edema (Hossmann et al. 1983) was the most probable cause of death. Gerbils that were lost during the later period of recirculation were not observed before dying, so the cause of death was not ascertained, among others, status epilepticus or delayed cerebral damage might have been responsible.

Biochemical Changes after Ischemia

Despite the similarly severe signs three types of biochemical patterns were found. The findings in the first group were the same as reported by others (Hossmann et al. 1981; Paschen et al. 1983) in gerbils with severe ischemia: acidic pH, total ATP depletion, and intensive NADH fluorescence in the whole ischemic heisphere (Fig. 2). During ischemia the lack of oxygen induces the anaerobic glycolytic pathway, and the accumulating lactate results in acidosis, the severity of which is proportional to the amount of lactate accumulated (Ljunggren et al. 1974). It was reported by Hope et al.(1987) that cerebral ischemia sufficient to reduce oxygen delivery to 75% of control values was associated with a fall in brain pH in lambs. However, during the reperfusion period in one case they found that brain pH had reverted to normal at a time when nuclear magnetic resonance indicated persistent elevation of brain lactate. Alkaline pH changes were reported by Kogure et al. (1980) in the center of the ischemic zone, where the highest tissue lactate concentration was found. However, in nonreperfused brains, similarly to others, we found only acidic areas. The adenylate energy charge decreases to minimal values after 5–7 min of complete ischemia. Thereafter no useful energy can be made available to ATP-requiring reactions (Lowry et al. 1964; Siesjö, 1981). The reduction of blood flow results in decreased oxygen availability and in consequence a disturbance of the cerebral redox state. The final increase in NADH depends on the actual flow rate: the lower the flow the higher the NADH concentration (Ginsberg et al. 1976).

In the second group pH decrease was found with ATP loss and increased fluorescence, where the acidic area was the most extended. Within acidic regions there were ATP-depleted areas with normal and increased NADH fluorescence as well. Similarly to our results (Fig. 7) Kim et al. (1985) also found in ischemic gerbil brains that the acidic area was greater than regions with decreased ATP and increased NADH content. Quantitative biochemical analysis from tissue samples was not carried out in our study, but, in a parallel work (submitted for publication) in rabbit brains after focal ischemia we showed that areas considered to be acidic according to their umbelliferone fluorescence contain lactate in significantly higher, while ATP and glucose in significantly lower concentrations (lactate: 22.94 mmol/kg, ATP: 0.99 mmol/kg, glucose: 1.24 mmol/kg) than areas with normal fluorescence. However, increased NADH fluorescence of the basal ganglia was found with normal ATP in the nonaffected hemisphere as well (Figs. 2 and 3), which can be considered as a methodological artifact or aspecific fluorescence.

In the third group the only finding was a relatively small acidic area in the frontal part of the affected hemisphere without any other metabolic changes. As this relatively small change resulted in severe clinical signs it can be concluded that functional impairment occurs at an earlier stage of ischemia than severe metabolic changes.

No changes in tissue potassium and hemoglobin were found in ischemic brains. Slight inhomogeneity in potassium staining of Figs. 2 and 5 was probably due to methodological artifacts. Blood within the brain quenches fluorescence (Welsh et al. 1978) and, thus, may contribute significantly to the tissue patterns of pH and NADH fluorescence. As no regional differences in hemoglobin were found after ischemia or after recirculation, the role of hemoglobin in the detected alterations of pH and NADH fluorescence can be excluded.

Branston et al. (1977) found that extracellular potassium rises sharply after the onset of ischemia.

Astrup et al. (1977) reported that extracellular potassium begins to rise if blood flow decreases below 8–10 ml/100 g per min, which is even lower than the threshold value for complete electric failure.

Mies et al. (1984) reported a decrease in potassium content after 2 h of focal ischemia in gerbil brains. Using the same technique we did not find any regional potassium differences between the hemispheres. At first sight this seems to be a contradiction. On the other hand, if cerebral blood flow is nearly zero, the potassium moved from the intracellular to the extracellular space, cannot be cleared from the tissue. As the method of Mies et al. (1984) reflected the total (intra- and extracellular) potassium content, no regional potassium changes would be expected with this almost zero level of regional blood flow. It cannot be excluded, however, that in a few cases blood flow was not reduced below the critical level causing potassium efflux.

So, in contrast to the findings of Paschen et al. (1983), we did not find close correlation between clinical signs and regional metabolic changes after the ischemic period. It should be emphasized that the duration of ischemia was much shorter in our study (30 versus 90 min). Severe signs with mild biochemical changes might be expected if a small lesion is located in a functionally important area (e.g., internal capsule) and/or besides local damage the function of the brain is depressed due to diaschisis as well. However, actual flow values might increase within the ischemic period (spontaneous reperfusion, Heiss et al. 1976) resulting in functional and metabolic recovery, or decrease further due to increasing edema causing progressive microcirculatory compression thereby aggravating the primary ischemic impact (Hossmann and Schuier 1980). It was reported in monkeys (Bell et al. 1985) that the duration of ischemia had a marked effect on edema formation: when ischemia was limited to 30 min, there was no significant edema, while extension of ischemia to 100 min produced a significant increase in cortical water content. So, a duration of focal ischemia between 30 and 90 min might be critical in producing closer correlation between clinical signs and the extent of regional metabolic changes.

Regional Changes after Recirculation

Gerbils having mild or no clinical signs at the end of ischemia and exhibiting total neurological and biochemical recovery were the most frequent finding after recirculation. Ischemic damage seemed to be reversible in these cases.

In the second group despite the clinical recovery, regional changes could be detected. Alkaline and acidic pH shift, potassium loss, and histological damage was observed in these cases after 4 and 8 days of recirculation. Alkaline areas were found by Paschen et al. (1985) in cat brains after focal ischemia followed by 2–48 h of recirculation.

The pH shifts can be explained by the discrepancy between the flow and the actual intensity of metabolism. Castaing et al. (1983) found alkaline areas in infarcted brain regions of humans in positron emission tomography studies. During the simultaneous measurement of regional blood flow, oxygen extraction, and metabolism, alkaline pH shift was found in areas with luxury perfusion (i.e., where the oxygen supply was overabundant relative to the metabolic needs of the brain tissue). The most likely explanation for the relationship between tissue alkalosis and luxury perfusion, is that the accumulated carbon dioxide and other metabolic wastes produced in the necrotic area by the remaining cells may be removed by overabundant local perfusion, and as a result the tissue content of these compounds, and in turn, the H^+ activity, will be lower than normal, thus resulting in alkalosis (Castaing et al. 1983). It was found recently (Kraig et al. 1987) that histologically proved irreversible tissue damage occurs if the pH decreases below 5.3. So, it can be supposed that irreversible tissue damage occurred if, during ischemia, the pH decreased below this critical level. The damaged tissue cannot maintain its acid-base homeostasis, and the pH of the tissue begins to rise from the normal brain pH 7.1–7.2 towards the more alkaline values of blood. The final pH is dependent on the stage of the tissue damage: necrotic areas are alkaline, while areas where the tissue remained alive or glial cells occupied the place of the necrotic tissue, the pH can return to normal values or acidosis may exist according to the momentary relationship between flow and metabolic intensity.

Tissue potassium decrease was reported by Welsh et al. (1982) following temporary ischemia in cat brains. In the reperfusion period the potassium might be washed out from the extracellular space and the damaged cells are not able to accumulate potassium again. On the other hand, neurons can be damaged in the reperfusion period too (delayed lesion, Kirino 1982), losing their ability to maintain their potassium homeostasis.

The metabolic changes were similar after 4 and 8 days of recirculation. Though no-reflow phenomenon (Ames et al. 1968) was reported to be an infrequent observation in the gerbil model (Nakai et al. 1977), its role cannot be excluded in these late changes. Postischemic hypoperfusion (Ito et al. 1980) may play a role as well as the maturation phenomenon (Ito et al. 1975) in the changes found after recirculation. The last assumption is supported by our obser-

vation (Fig. 6), where histological alteration was seen in the basal ganglia and the parietal cortex, similarly to the findings of Ito et al. (1975).

It should be emphasized that 30 min of occlusion does not necessarily mean 30 min of ischemia: if spontaneous reperfusion (Heiss et al. 1976) occurs, it is less, while in the case of postischemic hypoperfusion or the no-reflow phenomenon it is more than 30 min. However, a 30-min occlusion may result, at least in some of the cases, in detectable, probably irreversible tissue damage even 8 days after the ischemic insult which fact should be taken into consideration during human carotid surgery.

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