Regional Cerebral Metabolism in Experimental Brain Infarction

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Hemodynamic alterations in focal cerebral ischemia are now well documented by numerous studies. Reduction of rCBF in the early stages of experimental infarction (2, 11, 13), perifocal hyperemia and vasoparalysis, related steal phenomena, and the luxury perfusion syndrome are now familiar findings—both in experimental conditions and in human cerebrovascular accidents (CVA) (5, 10). Underlying and concomitant metabolic disturbances have been studied only recently (2, 4, 7, 8, 11). Little is known, however, about regional metabolic changes in focal cerebral ischemia.

Method

Embolic infarction was therefore produced in 26 mongrel dogs using the technique described by Molinari (9). Immediately following embolization, Evan's blue was injected. For metabolic studies, nine dogs—all of them showing severe neurologic disturbances—were sacrificed 24 hr later by immersing the heads into liquid nitrogen during maintained circulation and artificial respiration. The frozen head was then cut in slices with a precooled saw. Tissue samples were analyzed by enzymatic methods. For comparative microscopic examinations 12 dogs were sacrificed after 6, 24, and 48 hr, respectively.

Results

The following data have been collected in this study: angiography, clinical course, postmortem findings, and metabolic parameters in different areas of the brain.

From our results we want to concentrate here upon three points:

1. After the acute onset cerebral infarction is a progressive process.
2. Metabolic alterations are not confined to the infarcted area, but involve the entire brain.
3. The common pathogenetic factor for (1) and (2) seems to be expanding brain edema.

The extent of infarction after 24 hr has been consistently overestimated in our study by macroscopic inspection. As seen by microscopic examination, the infarcted area—with ischemic cell lesions and entire loss of nerve cells—is surrounded by a border of cells with initial hypoxic changes, which, however, are not yet permanently damaged. It is interesting to note that the diameter of this borderline zone shrinks during the first two days following acute infarction: From 4 to 5 mm after 6 hr it is reduced to 1.5 to 2 mm after 24 hr and disappears almost entirely after 48 hr. These time-dependent changes imply, in our opinion, a gradual expansion of the necrotic area or, in other words, a progression of the infarction during this interval.

For metabolic studies tissue samples were taken from the infarction and the perifocal zone, from a distant area of the same side, and from corresponding regions in the contralateral hemisphere.

In the area that we considered as infarcted by macroscopic inspection glucose and energy-rich phosphates are indeed significantly reduced, but not entirely lost (Fig. 1). The remaining
concentrations represent glucose and energy metabolism of the cells in the borderline zone just described. Although anaerobic glycolysis is evidenced by the high lactate level, the presence of phosphocreatine indicates that some aerobic metabolism must have been preserved, because phosphocreatine cannot be restored by anaerobic glycolysis (6). rCBF studies in experimental cerebral ischemia have indeed shown that some blood flow is left in the early stages of infarction (11, 13).

Less pronounced but still significant metabolic changes occur in the perifocal zone and in a distant area of the same hemisphere, which appeared normal on macroscopic inspection, indicating severe metabolic depression of this entire side of the brain. If we now turn to the contralateral hemisphere, there too glucose as the main source of energy production is somewhat diminished, although this does not affect the stationary levels of phosphocreatine and ATP. There is, however, a tendency for lactate elevation in this unaffected hemisphere, too. This does not necessarily imply anaerobic glycolysis, because lactate is known to diffuse freely in the extracellular space in this condition. However, if we look at the lactate/pyruvate ratio (Fig. 2), which is taken as a parameter of the redox state of the cytoplasmic NADH/NAD+ system, we find this ratio significantly elevated. The subnormal values of the phosphocreatine/creatine ratio and the energy charge potential, a measure of the balance between the rate of utilization and the rate of energy production (1), also suggest some metabolic depression in the contralateral hemisphere. This would then be in accordance with Meyer's findings in human CVA (7).