NEUROPATHOLOGICAL ALTERATIONS IN RAT BRAIN AFTER COMPLETE ISCHEMIA DUE TO RAISED INTRACRANIAL PRESSURE

James B. Brierley, Bengt Ljunggren, Bo K. Siesjö

Introduction

The maximum period of total ischemia that the brain can endure without irreversible damage remains ill-defined. Clinical observations, as well as a number of experimental results, indicate that cellular damage occurs if the period of ischemia is longer than 5-7 min (1,2,3,4). However, as recovery of neuronal function has been reported to occur following ischemia of considerably longer duration, using models that either remove blood from the brain (5) or prevent its stagnation during ischemia (6), it has been assumed that survival of brain cells is partly limited by failure of recirculation of the tissue after the termination of the ischemia.

The present communication describes a neuropathological study of the rat brain after complete ischemia of up to 15 min duration followed by a recirculation period of 30 min. In order to counteract any postischemic vascular factors that might interfere with complete recirculation of the brain, a model was used in which cerebral circulatory arrest was induced by means of an abrupt elevation of the cerebrospinal fluid pressure to a level above systemic arterial pressure (5). This model prevents blood from stagnating in the cerebral vasculature during the ischemic interval and allows an immediate return of an adequate perfusion pressure as soon as the intracranial pressure is reduced (7, 8). Previous biochemical data from this model have shown that when the tissue is recirculated following ischemia of 1-15 min duration, there is complete normalization of the tissue concentrations of lactate and of AMP (adenosine monophosphate) (8). This should exclude the possibility of any significant unperfused areas remaining in the tissue (9).

Methods

Male Wistar rats (300-400 g) were initially anaesthetized with di­vinyl ether, tracheotomized, immobilized with tubocurarine chloride, artificially ventilated, and then maintained on 70% N₂O and 30% O₂ so as to give arterial CO₂ tensions of 35-40 mm Hg and O₂ tensions exceeding 100 mm Hg. Complete cerebral ischemia was induced by infusing an artificial CSF into the cisterna magna until the CSF pressure exceeded the systolic arterial blood pressure. A double-barreled cannula was used to infuse the artificial CSF and simultaneously measure the intracranial pressure through the experimental procedure. The needle was supported by being introduced through the neck

This study was supported by grants from the Swedish Medical Research Council (Projects No. 14X-263 and 14X-2179), from the Swedish Bank Tercentenary Fund and from U.S. PHS Grant No. 5 RO1 NS 07838-05 from NIH.

167

N. Lundberg et al. (eds.), Intracranial Pressure II
© Springer-Verlag Berlin Heidelberg 1975
muscles (reflected downwards from the occiput) with the atlanto-occipital membrane exposed. Insertion of the tip of the needle into the cisterna magna was visually controlled. The CSF was preequilibrated with 5% CO₂ and maintained at 37°C. An excessive increase in systemic arterial pressure with the subsequent development of lethal pulmonary oedema was prevented by the simultaneous intravenous infusion of Arfonad (10). In all animals, the body temperature was kept close to 37°C and the brain temperature was prevented from falling (7).

Total cerebral ischemia was induced in a total of 24 animals, divided into 4 groups, for periods of 6 (n=5), 7.5 (n=5), 10 (n=8), and 15 (n=6) min per group. Ischemia was terminated by reducing the CSF pressure to normal. Recirculation was allowed for 30 min. before the brains were fixed by in vivo perfusion with FAM (formaldehyde, glacial acetic acid, absolute methanol, 1:1:8) through the ascending aorta after brief wash-out of the cephalic circulation with physiological saline. Both solutions were perfused at a pressure of 120 mm Hg for a total period of 25 min. The brains, removed 4 hours later, were stored in FAM at 4°C for at least 7 days. After slicing the forebrain in the coronal plane and the hindbrain in the mid-sagittal plane, paraffin sections were stained with cresyl violet and with cresyl violet combined with luxol fast blue.

Neuropathological observations

After ischemia of 6 and 7.5 min the brains of all animals were macro- and microscopically normal. In 7 of 8 animals after 10 min of ischemia and 6 of 6 animals after 15 min of ischemia, there were a few instances of ischemic neuronal alterations. These were restricted to the cerebral cortex and/or hippocampus, but were seen also in the striatum of one "15 minute animal". There were no significant left-right differences, and none between the 15 and 10 min animals. In the cerebral cortex ischemic neurons occurred in the third layer and to a lesser extent in the fifth and sixth layers. In the hippocampus they were seen in the Sommer sector (h 1) and in the end-folium (h 3-5). In the striatum only the small polymorphic elements were involved.

The neuronal alterations consisted of the earlier stages of the process termed ischemic cell change. The earliest stage, microvacuolation (11), was seen in the hippocampus (Fig. 1), while transitional stages up to and including that of typical ischemic cell change were seen in the cerebral cortex (Fig. 2 and 3) and striatum. Appearance in white matter, glial elements and blood vessels were normal.

Discussion

In view of the presence of unequivocal ischemic neuronal alterations after a circulatory arrest of 10 min and their absence after an arrest of 7.5 min, it is evident that the threshold or critical duration for the production of damage must lie between the two figures. In view of the relatively small numbers of neurons showing ischemic change after 15 as well as 10 min arrest, it is most probable that clinical recovery would eventually have been complete in both groups of animals.

The neurons exhibiting ischemic change did not occur at random but