REGULATION OF CEREBRAL BLOOD FLOW (CBF) DURING HYPOXIA AND EPILEPTIC SEIZURES

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INTRODUCTION

The exact mechanism as how cerebral vessels are dilated and CBF increases during arterial hypoxia and epileptic seizures is still poorly understood (Kuschinsky and Wahl, 1978; Winn et al., 1981a; Dőra, 1984a). Because recently it was suggested that adenosine may fulfill a critical role in the regulation of CBF (Winn et al., 1981a), and Jöbsis (1977) postulated cytochrome oxidase as being responsible for the dilatation of cerebral vessels during hypoxia, the present study was devoted to get further data on these issues.

METHODS

The experiments were carried out on cats anaesthetized with 50-60 mg/kg alpha-D-glucocloralose, immobilized with flaxedil, and artificially ventilated. Arterial blood gases and pH determined in the normoxic animals during the control period were in the physiological range. The heads of the animals were mounted in stereotaxic stands and a cranial window was made into the right parietal bone. The cranial window, described previously (Dőra, 1984a), was used to superfuse the brain cortex with various drugs, and for optical monitoring of cerebrocortical microcirculation and NADH fluorescence. Electrical activity of the exposed cortex and the other brain hemisphere was measured by silver electrodes built in the plastic ring of the cranial window and by copper screws fixed into the left parietal bone. Intracranial pressure was measured by metal tubes sealed also into the plastic ring of the cranial window. Intracranial pressure and arterial blood pressure were measured by Statham P23/d electromanometers.
Cerebrocortical reflectance (sum of scattered and reflected light) and NADH fluorescence were measured at 366 nm and 450 nm, respectively, through the cranial window with a microscope fluororeflectometer (Kováč et al., 1983; Döra, 1984a). Cerebrocortical vascular volume (CVV) and mean transit time of cortical blood flow (tm) were measured, CBF calculated, with the modified (Döra, 1984b) method of Eke et al. (1979). The reference values of these parameters were regarded as 100%.

For superfusion of the brain cortex, the artificial cerebrospinal fluid (mock CSF) of Wahl and Kuschinsky (1976) was used. The various drugs were dissolved in mock CSF, bubbled with 5% CO₂ balanced in air and thermostated at 38°C. For perfusion a 2-channel Harvard infusion pump with a perfusion rate of 1 ml/min was used. The pH of the CSF containing various drugs, except the CSF containing cyanide, was the same as the pH of the mock CSF (pH 7.20-7.25).

Experimental Procedures and Analysis of the Data

In the first series of experiments, the vasodilative potencies of the mitochondrial electron transport inhibitor amytal (inhibits at site I) and cyanide (inhibits at site III) were compared. Both drugs were applied by superfusion into the brain cortex.

In the second series of experiments, the vasodilative potency of topically applied adenosine and 2-chloroadenosine was tested. 2-chloroadenosine is a stable analogue of adenosine. It is not deaminated by adenosine deaminase and is taken up less rapidly by the brain as compared to adenosine (Winn et al., 1981b).

In the third series of experiments, it was tested how topically applied adenosine deaminase (5 U/ml) affects the hypoxic and functional hyperemic responses of cerebrocortical vessels. 5 U/ml adenosine deaminase deaminates 5x10⁻⁶ mol/ml/min adenosine into the nonvasoactive inosine. This enzyme activity is more than necessary to deaminate the extracellularly released adenosine, because during profound arterial hypoxia and epileptic seizures extracellular adenosine concentration in the brain does not increase to a higher value than approximately 10⁻⁸ mol/ml (Winn et al., 1981a).

In the fourth series of experiments, in order to get further insight into the significance of adenosine in the regulation of CBF, the brain cortices were topically treated with the vascular adenosine receptor antagonist theophylline (10⁻⁷ mol/ml). In the third and fourth series of experiments, arterial hypoxia, lasting some 3-4 min, was evoked by ventilating the animals with a gas mixture containing 6% oxygen. Epileptic seizures, lasting some