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16⁴⁸-17⁰⁶ SZ 3.2

ROLE OF EICOSANOIDS IN CEREBRAL BLOOD FLOW

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17⁰⁶-17²⁴ SZ 3.3

DO CYCLOOXYGENASE ENZYME PRODUCTS REGULATE FUNCTIONAL HYPEREMIA ASSOCIATED WITH SPREADING DEPOLARIZATION?

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17²⁴-17⁴² SZ 3.4

ENDOTHELIAL NITRIC OXIDE CONTRIBUTES TO NEUROVASCULAR COUPLING IN THE MOUSE SOMATOSENSORY CORTEX

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17⁴²-18⁰⁰ SZ 3.5

IMPACT OF DIET ON MICROVASCULAR FUNCTION AND METABOLITES OF ARACHIDONIC ACID

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Plenáris előadás

ŐSSEJT VÁLASZOK REGULÁCIÓJA RACIONÁLISAN TERVEZETT PHARMAKONOKKAL

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Department of Physiology, University of Tennessee Health Science Center

Szimpózium (SZ 4) 9¹⁰-10⁴⁰

NEUROPEPTIDEK SZABÁLYOZÓ SZEREPE A KÖZPONTI IDEGRENSZERBEN

Elnökök: **Helyes Zsuzsanna és Pintér Erika**

9¹⁰-9³³ SZ 4.1

AZ ANYAI VISELKEDÉS SZABÁLYOZÁSÁNAK ÚJ PEPTIDERG MECHANIZMUSAI

DO CYCLOOXYGENASE ENZYME PRODUCTS REGULATE FUNCTIONAL HYPEREMIA ASSOCIATED WITH SPREADING DEPOLARIZATION?

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Recurrent spreading depolarizations (SDs) occur spontaneously in the ischemic brain, are coupled with typical changes in local cerebral blood flow (CBF), and have been recognized to promote ischemic lesion progression. The regulation of the SD-related CBF response appears to be rather complex, and the discrimination of individual mediators poses a considerable challenge. Similar to neurovascular coupling to somatosensory stimulation, arachidonic acid metabolites could possibly play a central role in mediating the CBF response to SD, because SD coincides with a considerable accumulation of arachidonic acid in the cortex, and a significant elevation of prostanoid concentration in the cerebrospinal fluid.

We set out to determine systematically whether cyclooxygenase -2 (COX-2) products - specifically prostaglandin E2 - or COX-1 derived metabolites contribute to the evolution of the SD-coupled hyperemia in the intact or the ischemic rat cerebral cortex.

Two cranial windows were prepared on the parietal bone of isoflurane-anesthetized Sprague-Dawley rats (n=65). Global forebrain ischemia was achieved by the permanent, bilateral occlusion of the common carotid arteries. Sham-operated rats served as non-ischemic controls. DC potential was acquired through a glass capillary microelectrode, and local CBF was measured with laser Doppler flowmetry in the rostral craniotomy. The cortex in the rostral craniotomy was incubated in drug solutions or vehicle (1.5% DMSO in aCSF) for 40 min prior ischemia induction or SD elicitation. The following drugs were applied topically: the selective COX-2 inhibitor NS-398 (100 μ M), the selective COX-1 inhibitor SC-560 (25 μ M), or the selective prostaglandin-E2 receptor (EP4) antagonist L161,982 (1 μ M). Four SDs were initiated in all groups in the caudal cranial window by 1 M KCl at 15 min intervals.

Ischemia significantly attenuated the peak of hyperemia and elongated the duration of hyperemia in response to SD in all treatment groups. EP4 receptor selectively reduced the amplitude of hyperemia associated with SD in the intact but not in the ischemic cerebral cortex. COX-1 inhibition increased the duration of SD-associated hyperemia with respect to vehicle under ischemia, as well as the duration of the SD-associated transient negative DC shift. The duration of the transient negative DC shift and that of the associated hyperemic response displayed a significant positive correlation.

We propose that the EP4 prostaglandin receptors located on cerebrovascular smooth muscle cells mediate the SD-related hyperemia in the intact cortex, but their contribution is overridden by other vasoactive mediators during ischemia. On the other hand, COX-1 products appear to usher the recovery from SD during ischemia, and thereby determine the duration of the SD-related hyperemia indirectly. Taken together, COX products appear to regulate the SD-associated CBF response through various pathways including EP4 receptor and COX-1 enzyme activation.