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Brief Report

Role of Local Nerves and Prostaglandins in Regulation of Basal Blood Flow and Hypercapnic Vasodilatation of Cerebral Blood Vessels in the Rabbit

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Abstract

The mechanisms underlying cerebral vasodilatation during hypercapnia are not fully understood. To examine the role of nerves and prostaglandins in the regulation of basal blood flow and in hypercapnia-induced vasodilatation in the cerebral blood vessels of rabbit. Cerebral blood flow was measured by laser Doppler flow-meter in 18 NZW rabbits anesthetized with sodium pentobarbital. Tetrodetoxin was administered locally and indomethacin (a prostaglandin inhibitor) both locally and systemically before and during induction of hypercapnia. Basal cerebral blood flow did not change significantly in response to local tetrodetoxin, and also after local and systemic administration of indomethacin. Hypercapnia increased cerebral blood flow by 25.9±3.9% before and by 24.3±6.5% after administration of TTX and by 22.1±7.1% before and by 18.2±6.3% after administration of indomethacin. In the rabbit, prostaglandin and regional nerves had no role in regulation of basal cerebral blood flow, nor did they contribute to cerebral vascular dilatation during hypercapnia.

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Keywords • Cerebral blood flow • hypercapnia • nerves • prostaglandins

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Introduction

Carbon dioxide is the most powerful metabolic factor contributing to auto-regulation of cerebral blood flow (CBF). The underlying mechanisms, however, are not fully understood; two potential mediators suspected are nerves and prostaglandins (PG). In rat, blockage of prevascular nerves by tetrodetoxin (TTX) has reduced the resting CBF (rCBF) by 23%[1] and neuronal nitric oxide synthase (NOS) inhibition by about 20%.[2] In contrast, some experiments have shown that sectioning the parasympathetic nerves had no effect on rCBF[3] and that local nerve lesions in rat did not affect the CBF's response to hypercapnia (hCBF).[4] Systemic of indomethacin has been shown to reduce rCBF[5] in rat. In contrast, some authors failed to show significant changes in rCBF by indomethacin in cat and dog.[6,7] Under hypercapnic conditions, indomethacin has diminished hCBF in piglets.[8] However, in another study Indomethacin had no effect on hCBF in cat.[6] This study was conducted to further evaluate the role of nerves and PGs in the regulation of

CBF at rest and in hypercapnic conditions.

Methods

Eighteen NZW rabbits (2-3 kg) were anaesthetized by sodium pentobarbital (30 mg/kg). A cannula was inserted into the femoral artery to measure arterial blood pressure and to take samples for obtaining P_{O2}, P_{CO2} and pH values. A pool was made over the cortex to superfuse continuously with artificial CSF (ACSF) bubbled with 5% CO_2 in 95% O_2[9]. Hypercapnia was induced by 6.5% CO_2 in a gas mixture of 25% O_2 and 68.5% N_2. TTX was dissolved in ACSF (20 µM). Indomethacin was initially dissolved in ethanol and then added to ACSF to reach a concentration of 1mM. A laser Doppler flow-meter (Moor Instruments; model MBF3D, UK) was used to assess the relative changes in CBF. In the first group (n=9), while the animals were on normal air (normocapnia) for 1 hour post surgery, the experiment was continued in four steps:

1- The animal was shifted to hypercapnia for 10 minutes, 2- The animal was shifted to normocapnia for 15 minutes followed by replacement of ACSF perfusate by TTX-containing ASCF for 30 minutes then the first two steps were repeated in the presence of local TTX.

In the second group (n = 9) the experiment was performed in seven steps, of which the first four steps were similar to those of the first group except that local indomethacin (1mM) was used instead of TTX at the end of step 2. The three additional stages were: 5- indomethacin (0.7mg/ml saline) was infused systematically for 30 minutes, 6- Hypercapnia was applied in the presence of systemic indomethacin for 10 minutes, 7-The animal was shifted to normocapnia (in the presence of systemic Ind) for 15 minutes.

At the end of each step BP and CBF were recorded and an arterial blood sample was collected.

Comparisons were performed using one-way ANOVA followed by Tukey's HSD test.

Results

rCBF showed a small reduction during local TTX superfusion. rCBF also showed non-significant changes during local or systemic Ind administration. Hypercapnia ($PaCO_2$ of 53 mmHg and pH 7.21) increased CBF by 25.9±3.9% before and by 24.3±6.5% after local TTX. Hypercapnia increased CBF by 22.1±7.1% before and by 18.2±6.3 % and 24.1±7.1% after local and systemic indomethacin, respectively. BP showed small, non-significant changes during local TTX as well as local and systemic indomethacin administration, or in response to hypercapnia. Resting Pco_2 and pH were 34.1±1.8 mmHg, and 7.43±0.03 respectively.

Discussion

Role of nerves and PGs in basal cortical blood flow regulation

TTX superfusion caused only a small change in rCBF it can be inferred that local nerves probably have no role in rCBF regulation in this vascular bed. This finding is in agreement with the results of other investigations on rats and piglets in which TTX or nerve section had no effect on rCBF.[3,8] However, the results are different from those showing that TTX or neuronal NOS inhibitor reduced rCBF in rat.[1,2] Moreover, superfusion and systemic infusion of indomethacin had no significant effect on rCBF, indicating that PGs did probably not have a significant role in rCBF regulation in rabbit. These findings suggest that apparently none of the factors regulating basal CBF operate through PGs in this animal. These results are in agreement with other studies on other animal species including cat[6] and dog[7], whereas it does not support the findings of Heinert and colleagues[5], which showed that Indomethacin reduced rCBF in rat. It seems that species and/or methodological differences might underlie the discrepancy among the findings of these studies.

Role of nerves and PGs in hypercapnic vasodilatation of cerebral blood vessels

The finding that there was no significant difference between hCBF increments in the presence and absence of TTX indicates that local nerves probably do not play a role in hypercapnic cerebral vasodilatation in the rabbit. This finding is in agreement with the results of Iadecola and colleagues in rat[4] in which they showed that destruction of local nerves originating from cerebellum was unable to reduce hCBF, but was different from the findings of some other investigators showing reduction in hCBF due to general local nerve inhibition by TTX or using a neuronal NO synthase inhibitor.[1,2] With respect to our data on the effect of local and systemic indomethacin on hypercapnic response, it may be concluded that PGs have no role in hypercapnic vasodilatation in this vascular bed. These findings are in agreement with those found in dog[7] in which PGs did not affect hCBF. However, in the studies of Parfenova et al in piglets[8] and Heinert et al[5] in rat, indomethacin did reduce hCBF. The differences might be due to species differences, different Pco_2 levels or different techniques of vasodilatation assessment in these studies.

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