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BRAIN RESEARCH

Research Report

Role of α-adrenoceptors and prostacyclin in the enhanced adrenergic reactivity of goat cerebral arteries after ischemia-reperfusion

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ABSTRACT

To analyze ischemia-reperfusion effects on the cerebrovascular adrenergic response, the left middle cerebral artery (MCA) of anesthetized goats was occluded for 120 min and reperfused for 60 min. Isolated segments from the left (ischemic) and right (control) MCA exhibited isometric constriction in response to noradrenaline (10^{-8}–10^{-4} M, in the presence of β-adrenoceptors blockade), phenylephrine (α_1-adrenoceptors agonist, 10^{-8}–10^{-4} M), B-HT-920 (α_2-adrenoceptors agonist, 10^{-7}–3×10^{-3} M) or tyramine (indirect sympatheticomimetic amine, 10^{-8}–10^{-4} M), but this constriction was greater in ischemic arteries. The cyclooxygenase (COX) inhibitor meclofenamate (10^{-5} M) augmented the response to noradrenaline only in control arteries. The prostacyclin (PGI_2) synthesis inhibitor tranylcypromine (TCP, 10^{-5} M) increased the response to noradrenaline in control arteries and reduced it in ischemic arteries. The thromboxane A_2 (TXA_2) synthase inhibitor furegrelate (10^{-6} M) did not modify the noradrenaline effect in both types of arteries, whereas the TXA_2 receptor antagonist SQ 29 548 (10^{-5} M) and the COX-2 inhibitor NS-398 (10^{-6} M) decreased the response to noradrenaline only in ischemic arteries. PGI_2 caused a small relaxation in control arteries and a small contraction in ischemic arteries. α-Adrenoceptors and COX-2 protein expression and the metabolite of PGI_2 were augmented in ischemic arteries. Therefore, ischemia-reperfusion may increase the cerebrovascular responsiveness to noradrenaline, through upregulation of α-adrenoceptors and increased COX-2-derived PGI_2 exerting a vasoconstrictor action. After ischemia-reperfusion, noradrenaline might increase PGI_2 production thus contributing to adrenergic vasoconstriction and/or PGI_2 would potentiate the noradrenaline effects.

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Abbreviations: MCA, middle cerebral artery; COX, cyclooxygenase; PGI_2, prostacyclin; TCP, tranylcypromine; TXA_2, thromboxane A_2; NPY, neuropeptide Y

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1. Introduction

Brain ischemia-reperfusion can produce damage and dysfunction of cerebral blood vessels, in addition to that of nervous tissue. There are studies showing that even short periods (≤30 min) of cerebral ischemia followed by reperfusion can induce endothelial dysfunction (Mayhan et al., 1988; Rosenblum, 1997) and longer periods (60 min) might also increase the endothelial production of vasoconstrictor prostanoids (Sánchez et al., 2006). These adverse effects of ischemia-reperfusion could alter the adrenergic response of cerebral vasculature. This might have significant implications for regulation of blood supply to ischemic-reperfused brain area as experimental and clinical cerebral ischemia can be accompanied by increased catecholamine levels in plasma (Hachinski et al., 1986) and cerebrospinal fluid (Meyer et al., 1974). This catecholamine release by acting on cerebral vasculature may be detrimental to the extent of brain ischemia (Nellgard et al., 1999). Both α_1-adrenoceptors antagonists, by inhibiting vascular smooth muscle contraction (He et al., 2008), and α_2-adrenoceptors agonists (Zhang, 2004) and antagonists (Gustafson et al., 1990) have been shown to lessen ischemia-induced neuronal damage.

Cerebral vasculature appears to receive a dense adrenergic innervation, and although the functional significance of this innervation remains to be a controversial topic, there are in vivo and in vitro studies suggesting that cerebral vasculature exhibits a basal adrenergic constrictor tone and constricts to exogenous and endogenous noradrenaline by direct α-adrenoceptors activation (Edvinsson and Krause, 2002; Goadsby and Edvinsson, 1997; Jordan et al., 2000). Recent evidence suggests that in humans sympathetic innervation produces a basal tone and vasoconstriction in cerebral vasculature (Van Lieshout and Secher, 2008) and that this innervation plays a role in cerebral autoregulation (Hamner et al., 2010). On the other hand, the contraction of cerebral arteries in response to noradrenaline may be modulated by the endothelium (Edvinsson and Krause, 2002). Studies to examine the effects of ischemia-reperfusion on cerebrovascular response to adrenergic stimulation are very few, and the available results are inconclusive. One study performed in anesthetized newborn pigs shows that 20 min of global cerebral ischemia induced by intracranial hypertension followed by 2–3 h or 24 h of reperfusion did not affect the reactivity of pial arteries in situ to topical application of noradrenaline (Leffler et al., 1989b). Another study in rats shows that the long-term inhibition of NO synthesis with L-NAME limits infarct expansion by a reduction in the vasoconstrictor response to noradrenaline and serotonin after prolonged occlusion of the left middle cerebral artery (MCA), without reperfusion (Sercombe et al., 2001).

The present study was performed to analyze the effects of ischemia-reperfusion on the cerebrovascular adrenergic reactivity, analyzing the role of α-adrenoceptors and prostanoids in this reactivity. Ischemia-reperfusion was induced in anesthetized goats by inducing 120-min occlusion of the MCA, followed by 60-min reperfusion, and vascular adrenergic response was examined in isolated arteries. Previous studies suggest that in the goat, adrenergic mechanisms are involved in the regulation of the cerebral circulation (Alborch et al., 1977; Diéguez et al., 1998), and that ischemia-reperfusion induces endothelial dysfunction (Sánchez et al., 2006; Salcedo et al., 2009).

2. Results

2.1. Hemodynamic changes during ischemia and reperfusion

In 29 animals, during MCA occlusion mean systemic arterial pressure was decreased by 12±2% ($p<0.01$), and it was further decreased by 16±2% during reperfusion ($p<0.01$). Heart rate during MCA occlusion and reperfusion was not significantly distinct from the control. In 10 of these animals, blood flow in the left MCA was abolished during arterial occlusion as expected. Immediately after the release of this occlusion, left MCA flow increased markedly, then it was progressively recovering and at 60 min after the start of reperfusion it remained increased by 44±11% ($p<0.05$). At this time, left MCA resistance was decreased by 27±6% ($p<0.01$). The hemodynamic values during control, left MCA occlusion and reperfusion are summarized in Table 1.

Systemic blood gases and pH did not change significantly during ischemia and reperfusion when compared to control conditions (these data are not shown).

2.2. In vitro arterial response

KCl (100 mM) contracted resting arteries, and this contraction was similar at the beginning and at the end of the experiments. Also, this contraction was not statistically different between control and ischemic arteries. Mean contraction was 2020±97 mg in control arteries (82 segments, 29 animals) and 1817±92 mg (79 segments, 29 animals) in ischemic arteries ($p>0.05$).

Noradrenaline (10^{-8}–10^{-4} M) produced a concentration-dependent contraction in control and ischemic arteries pretreated with propranolol (10^{-7} M). The sensitivity to noradrenaline was similar in both types of arteries, but the

Table 1 – Values for mean systemic arterial pressure, middle cerebral artery (MCA) flow, MCA resistance and heart rate obtained in 29 anesthetized goats under control conditions at the end of the MCA arterial occlusion (ischemia) and at 60 min of reperfusion.

	Control	Ischemia	Reperfusion
Mean arterial pressure (mm Hg)	113±2	99±2 **	95±1 **
MCA flow [a] (mL min^{-1})	2.62±0.15	0	3.78±0.5 *
MCA resistance [a] (mm Hg mL^{-1} min)	44±2.36	∞	32±4.31 **
Heart rate (beats min^{-1})	77±2	77±3	79±3

Values are mean±SEM.
[a] The values correspond to 10 of the 29 animals.
** $p<0.01$ compared with its control.
* $p<0.05$ compared with its control.