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Charakterization of bradykinin-induced vasomotor actions in cerebral and peripheral arteries after focal brain ischemia in rats

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Bradykinin (BK), a mediator of the kallikrein-kinin system (KKS) is a highly potent vasoactive nonapeptide, the release of which is greatly enhanced in inflammatory responses. Under physiological condition, BK affects cerebral arterial tone acting upon B2 or / and B1 receptors. In this study, we aim to explore the influence of acute brain ischemia on the BK-related responses in both intracranial and extracranial arteries, and also to identify the possible underlying mechanisms.

Focal brain ischemia was induced in male Sprague-Dawley rats using the intraluminal filament approach to elicit either transient middle cerebral artery (MCA) occlusion (2 hours followed by 22 hours of reperfusion) or permanent MCA occlusion (24 hours). Vascular reactivity was measured in ring segments mounted in organ bath, and the change of isometric force to BK application and/or other reagents was recorded.

In arteries obtained from control animals, BK did not induce any significant vasomotor response in the MCA and elicited only a small relaxation in the basilar artery (BA) at a high concentration (10 µM). In peripheral arteries, BK did not evoke any response in the coronary artery (CA) and elicited a concentration-related contraction in the saphenous artery (SA). Following transient MCA occlusion BK induced a *de novo* concentration-related endothelium-dependent relaxation in the ipsilateral MCA which was lost after endothelial cells removal. Although both B1 and B2 receptor mRNA was detectable after transient MCAO, the BK-induced relaxation was mediated by activation of B2 receptors exclusively. Using specific inhibitors it was found that the BK-induced relaxation was mediated by release of nitric oxide (NO) and endothelium-dependent hyperpolarization (EDH) due to opening of intermediate conductance Ca^{2+}-activated K^+ (IK_{ca}) channels. Strikingly, in segments from the contralateral MCA BK also elicited a *de novo* concentration-related vasodilatation mediated by activation of B2 receptors, though the maximum effect was smaller and the threshold concentration markedly higher than in the ipsilateral MCA. BK did not induce any response in CA and produced a dose-related contraction in SA. Notably, this BK-induced contraction was significantly decreased compared to control conditions in the segments obtained from the paretic side.

After permanent MCA occlusion, BK also induced a *de novo* concentration-dependent relaxation in the ipsilateral MCA, again mediated *via* B2 receptor activation. However, the absolute value of relaxation was considerably smaller than after transient MCAO, and no response to BK was observed in the contralateral MCA at all. Similar to transient MCAO, BK did not evoke any vasomotor effect in CA ring segments, but induced dose-related contractile responses in SA segments from both sides.

In conclusion, our results indicate profound change of vessel functions and underlying receptor expression to BK following acute focal brain ischemia. Accordingly, BK may be added to a list of agonists including endothelin-1, angiotensin II, and 5-HT which are characterized by profound alterations in their vasoactive efficacy under pathological conditions.