ATP-Sensitive Potassium Channels in the Basilar Artery During Chronic Hypertension

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We examined the hypothesis that dilatation of the basilar artery in response to activation of ATP-sensitive potassium channels is impaired in stroke-prone spontaneously hypertensive rats (SHRSP). Changes in basilar artery diameter in response to aprikalim, a direct activator of ATP-sensitive potassium channels, were measured in anesthetized SHRSP and normotensive Wistar-Kyoto (WKY) rats through a cranial window. Topical application of aprikalim increased basilar artery diameter in WKY rats. Glibenclamide, a selective inhibitor of ATP-sensitive potassium channels, abolished aprikalim-induced vasodilatation. Thus, ATP-sensitive potassium channels are functional in the basilar artery of WKY rats in vivo. Aprikalim (10^{-6} mol/L) dilated the basilar artery by 31±5% (mean ± SEM) in WKY rats but only 5±1% in SHRSP. The concentration-response curve to aprikalim in SHRSP was significantly shifted to the right, but the response to the highest concentration of aprikalim (10^{-5} mol/L) was similar in SHRSP and WKY rats. Vasodilatation in response to norepinephrine was also impaired in SHRSP. Dilator responses of the basilar artery to forskolin, a direct activator of adenylate cyclase, and nitroprusside, a direct activator of guanylate cyclase, were normal in SHRSP. The findings suggest that dilatation of the basilar artery in response to direct activation of ATP-sensitive potassium channels is impaired in SHRSP compared with WKY rats in vivo. (Hypertension. 1993;22:677-681.)

Key Words • cerebral arteries • forskolin • norepinephrine • potassium channels • rats, inbred SHR

Vasodilator responses are impaired in several models of experimental hypertension.1-3 Impairment of endothelium-dependent responses during chronic hypertension has been described both in vitro1-6 and in vivo.7-8 In contrast, endothelium-independent vasodilator responses are generally considered to be normal in hypertensive animal models.2,3,9 Most previous studies of endothelium-independent mechanisms in hypertension have focused on responses to activation of guanylate cyclase, especially in response to nitrovasodilators, or activation of adenylate cyclase. Another major mechanism of vasodilatation involves hyperpolarization of smooth muscle, which can be produced by activation of several types of potassium channels.10

Aprikalim, a direct activator of ATP-sensitive potassium channels, dilates the basilar artery in vivo,11 which suggests that ATP-sensitive potassium channels are functional in the basilar artery. The effect of chronic hypertension on the activity of ATP-sensitive potassium channels in cerebral blood vessels is not known. The first goal of this study was to test in vivo the hypothesis that dilatation of the basilar artery in response to activation of ATP-sensitive potassium channels by aprikalim is altered during chronic hypertension. We examined responses of the basilar artery to aprikalim in stroke-prone spontaneously hypertensive rats (SHRSP).

We have reported recently that dilator responses of the basilar artery to norepinephrine and forskolin in vivo are mediated in part by activation of ATP-sensitive potassium channels.12 Thus, a cyclic AMP (cAMP)-dependent mechanism may be involved in activation of these potassium channels. The second goal of the present study was to examine the hypothesis that altered activity of ATP-sensitive potassium channels may affect responses of the basilar artery to norepinephrine and forskolin in SHRSP.

Methods

Animal Preparation

Male Wistar-Kyoto (WKY) rats (386±7 g, n=15) and SHRSP (335±5 g, n=15) (6 to 9 months old) were anesthetized with pentobarbital sodium (50 mg/kg IP). The trachea was cannulated, and the animals were mechanically ventilated with room air and supplemental oxygen. Skeletal muscle paralysis was produced with gallamine triethiodide (5 to 10 mg/kg). Anesthesia was supplemented regularly at 20 to 25 mg/kg per hour. Depth of anesthesia was evaluated by applying pressure to a paw or the tail and observing changes in heart rate or blood pressure. When such changes occurred, additional anesthetic was administered. Catheters were placed in both femoral arteries to measure systemic
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Experimental Protocol

We examined responses of the basilar artery to topical suffusion of aprikalim \((10^{-7} \text{ to } 10^{-5} \text{ mol/L})\), forskolin \((10^{-10} \text{ to } 10^{-5} \text{ mol/L})\), norepinephrine \((10^{-8} \text{ to } 10^{-3} \text{ mol/L})\), and sodium nitroprusside \((10^{-4} \text{ to } 10^{-6} \text{ mol/L})\). Agonists were mixed in artificial cerebrospinal fluid and suffused over the craniotomy for 5 minutes. Basilar artery diameters were measured immediately before and during the last minute of application of each agonist. After application of each agonist, the artery returned to baseline diameter within a few minutes before application of a subsequent agonist. The application sequence of agonists was randomized. Glibenclamide \((10^{-4} \text{ mol/L})\) was suffused 5 minutes before and during application of agonists. Glibenclamide and aprikalim were dissolved in dimethyl sulfoxide. Control experiments were performed in the presence of the vehicle, 0.05% dimethyl sulfoxide.

Statistical Analysis

All values are expressed as mean±SEM. An unpaired \(t\) test was used to compare absolute values under control conditions and during interventions, and Wilcoxon's test was used to compare percentage changes. A value of \(P<.05\) was considered significant.

Results

Mean arterial pressure was 95±5 mm Hg in WKY rats and 203±10 mm Hg in SHRSP. Under control conditions, baseline basilar artery diameter was smaller in SHRSP \((209±6 \text{ µm})\) than in WKY rats \((277±19 \text{ µm})\) \((P<.05)\).

Responses to Aprikalim

In WKY rats, topical application of aprikalim increased basilar artery diameter, with a maximum response of 44±4% \((P<.05)\) (Fig 1). Application of glibenclamide \((10^{-4} \text{ mol/L})\) alone for 5 minutes did not produce any significant change in basilar artery diameter \((P>.05)\) but almost completely inhibited dilatation of the basilar artery in response to aprikalim \((P<.05)\) (data not shown). Thus, ATP-sensitive potassium channels are functional in the basilar artery of WKY rats in vivo. The findings are similar to those observed in Sprague-Dawley rats.\(^{11}\)

In SHRSP, the concentration-response curve of the basilar artery to aprikalim was shifted to the right compared with that in WKY rats \((P<.05)\). Aprikalim \((10^{-4} \text{ mol/L})\) dilated the basilar artery by 31±5% in WKY rats but only 5±1% in SHRSP \((P<.05\text{ versus WKY rats})\). The response to the highest concentration of aprikalim \((10^{-5} \text{ mol/L})\), however, was similar in SHRSP and WKY rats \((P<.05)\).

Responses to Forskolin, Norepinephrine, and Nitroprusside

Dilatation of the basilar artery in response to norepinephrine and forskolin appears to be mediated in part by activation of ATP-sensitive potassium channels.\(^{12}\) We examined responses of the basilar artery to norepinephrine and forskolin in SHRSP and WKY rats. Norepinephrine caused marked vasodilatation in WKY rats, and the response was impaired significantly in SHRSP \((P<.05)\) (Fig 2). In contrast, forskolin produced similar dilatation of the basilar artery in WKY rats and SHRSP \((P>.05)\). Responses of the basilar artery to sodium nitroprusside were similar in WKY rats and SHRSP \((P>.05)\).

Discussion

There are three major new findings in the present study. First, dilatation of the basilar artery in response to aprikalim is impaired in SHRSP in vivo. Thus, activity of ATP-sensitive potassium channels in the basilar artery is altered during chronic hypertension. Second, dilatation of the basilar artery in response to forskolin is not impaired in SHRSP in vivo. Thus, activation of ATP-sensitive potassium channels in the basilar artery by a CAMP-dependent mechanism may not be impaired during chronic hypertension. Third, dilatation of the basilar artery in response to norepinephrine, which may be mediated in part by activation of ATP-sensitive potassium channels, is impaired in SHRSP.

Altered Responses to Aprikalim

Aprikalim, a direct activator of ATP-sensitive potassium channels,\(^{13}\) dilates the basilar artery (see Refer-
Dilator responses of the basilar artery to norepinephrine and calcitonin-gene-related peptide are mediated in part by activation of ATP-sensitive potassium channels. Thus, activation of ATP-sensitive potassium channels may be an important mechanism by which cerebral arteries respond to endogenous vasodilator stimuli. Acetylcholine appears to produce relaxation in cerebral arteries that is mediated by release of both endothelium-derived relaxing factor and an endothelium-derived hyperpolarizing factor that activates ATP-sensitive potassium channels. Endothelium-dependent hyperpolarization of vascular muscle in response to carbachol is impaired in the aorta of renal hypertensive rats. Endothelium-dependent hyperpolarization in response to acetylcholine but not to cromakalim is impaired in the mesenteric artery in spontaneously hypertensive rats. In the mesenteric artery, hyperpolarization is mediated by activation of tetraethylammonium-sensitive potassium channels, which differ from ATP-sensitive potassium channels, and impaired hyperpolarization appears to be due to reduced production of an endothelium-dependent hyperpolarizing factor. There are no data, however, regarding alterations in vascular responses to direct activation of potassium channels during chronic hypertension in vivo or in the cerebral circulation.

In the present study, we found marked impairment of dilator responses of the basilar artery to submaximal concentrations of aprikalim in SHRSP. These findings suggest that chronic hypertension may alter the affinity of ATP-sensitive potassium channels to aprikalim in the basilar artery. Vasodilatation in response to the highest concentration of aprikalim tested was not significantly different in SHRSP and WKY rats. Although we did not examine maximum responses of these potassium channels, the number of ATP-sensitive potassium channels may not be reduced in SHRSP. Thus, we suggest that the affinity of ATP-sensitive potassium channels but not the number may be reduced in SHRSP.

It is very likely that aprikalim produces dilatation of the basilar artery by activation of ATP-sensitive potassium channels in vascular muscle. Responses to aprikalim are inhibited by glibenclamide, a selective inhibitor of ATP-sensitive potassium channels. Dilatation of cerebral vessels in response to aprikalim is not attenuated by an inhibitor of nitric oxide synthase or inhibitors of other potassium channels (apamin and charybdotoxin). In the present study, we used WKY rats as control animals to compare with SHRSP. Impaired responses of the basilar artery to aprikalim in SHRSP are probably related to chronic hypertension. We cannot exclude the possibility, however, that differences in response to aprikalim are related to genetic differences between WKY rats and SHRSP that are unrelated to hypertension.
The number of β-adrenergic receptors appears to be diminished in aorta of spontaneously hypertensive rats. Because forskolin-induced dilatation of the basilar artery is similar in SHRSP and WKY rats, it appears that the cAMP-dependent mechanism is intact. Thus, impaired responses of the basilar artery to norepinephrine in SHRSP may also be due to a reduced number of β-receptors. We also cannot exclude the possibility that increased expression of α-adrenergic receptors may contribute to reduced vasodilator responses to norepinephrine in SHRSP.

In summary, dilator responses of the basilar artery to aprikalim, a direct activator of ATP-sensitive potassium channels, are impaired in SHRSP in vivo. This impairment may be due to a reduced affinity of the potassium channels to aprikalim. Forskolin-induced vasodilation was not impaired in SHRSP. These findings suggest that responsiveness of potassium channels to a cAMP-dependent mechanism, which seems to occur at a different site than activation by aprikalim, may not be impaired during chronic hypertension.

Acknowledgments

This study was supported by grants HL-38901, HL-16066, NS-24621, HL-14388, and AG-10269 from the National Institutes of Health, Bethesda, Md; by research funds from the Veterans Administration; and by a grant-in-aid from the American Heart Association (92015170). F.M.F. is an Established Investigator of the American Heart Association. We thank Rhone-Poulenc Rorer (France) for the supply of aprikalim.

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Hypertension. 1993;22:677-681
doi: 10.1161/01.HYP.22.5.677

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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