Mechanism of Extracellular $K^+$-Induced Local and Conducted Responses in Cerebral Penetrating Arterioles

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**Background and Purpose**—Extracellular concentration of potassium ion ([K$^+$]$_o$) may have a significant influence on the cerebral circulation in health and disease. Mechanisms of [K$^+$]$_o$-induced conducted vasomotor responses in cerebral arterioles, possibly linking microvascular regulation to neuronal activity, have not been examined.

**Methods**—We analyzed vascular responses to small increases of [K$^+$]$_o$ (up to 5 mmol/L) in isolated, cannulated, and pressurized rat cerebral arterioles (36.5±1.4 μm). [K$^+$]$_o$ was elevated globally through extraluminal application or locally through micropipette, while arteriolar diameter was measured online.

**Results**—Elevation of [K$^+$]$_o$ (5 mmol/L) produced dilation that was inhibited by ouabain but not BaCl$_2$. Locally applied [K$^+$]$_o$ (3 to 5 mmol/L) produced a biphasic response (initial constriction followed by dilation), both of which were conducted to the remote site (distance 1142±68 μm). Endothelial impairment inhibited conducted but not local biphasic responses. Extraluminal ouabain attenuated local and conducted secondary dilation but not initial constriction. The local biphasic response was unaffected by extraluminal or intraluminal BaCl$_2$. Extraluminal but not intraluminal BaCl$_2$ impaired both conducted constriction and dilation.

**Conclusions**—In rat penetrating arteriole, (1) [K$^+$]$_o$ (3 to 5 mmol/L) strongly regulates arteriolar tone and causes conducted vasomotor responses; (2) local responses to elevated [K$^+$]$_o$ are endothelium independent but conducted responses are dependent on an intact endothelium; (3) smooth muscle Na$^+$-$K^+$-ATPase activation is the generator of conducted dilation; and (4) smooth muscle inward rectifier potassium channels sustain conduction. Our findings suggest that potassium-induced conducted vasomotor responses may link local neuronal activity to microvascular regulation, which may be attenuated in pathological conditions. (Stroke. 2002;33:2692-2699.)

**Key Words:** endothelium ■ microcirculation ■ potassium ■ rats

Vasomotor responses to physiological substances travel millimeters upstream and downstream along arteriolar blood vessels from the site of local stimulation. Such conducted vasomotor responses may be an important mechanism to adjust microvascular blood flow precisely to local tissue needs.1-3 These conducted responses are characterized by a high conductivity velocity, suggesting that the conduction results from the electrotonic spread of altered membrane potential via gap junctions.2,4 In the arteriolar wall, gap junctions connect neighboring endothelial and smooth muscle cells, as well as endothelial cells and smooth muscle cells.4,5

In the cerebral microcirculation, we demonstrated that vasoactive substances such as ATP and adenosine stimulated conducted response of rat penetrating arterioles.1,6 The conduction of vasomotor responses in cerebral penetrating arterioles may contribute to the matching of metabolic demand of tissue and regulate regional blood supply at increased neuronal activity.7 On the basis of this anatomic relationship, the penetrating arteriole can communicate with surrounding brain tissue7,8 to supply an appropriate blood flow into the capillary bed.

Extracellular concentration of potassium ion ([K$^+$]$_o$) has been implicated as a regulator of the link between neuronal activity and regulation of blood flow.5-10 [K$^+$]$_o$ is regulated by neuronal and glial mechanisms.11,12 Potassium ions released from active neurons may be transported by astrocytes onto arterioles,9 affecting blood flow. Small increases in [K$^+$]$_o$ cause vasodilation via stimulation of electrogenic Na$^+$-$K^+$ pump and/or inward rectifier K$^+$ (KIR) channels in cerebral artery and arteriole.5,9,13,14

In this study we examined effects of globally elevated [K$^+$]$_o$ (5 mmol/L) via extraluminal application (global [K$^+$]$_o$) and locally elevated [K$^+$]$_o$ (3 to 5 mmol/L) via microapplication (local [K$^+$]$_o$) in isolated, cannulated, and pressurized cerebral penetrating arterioles. The effects of local [K$^+$]$_o$ were designed to simulate potassium release as it might occur in response to neuronal stimulation.

**Materials and Methods**

Procedures in this study were reviewed and approved by the Institutional Animal Care and Use Committee at Washington University.
Isolated Vessel Preparation
Penetrating cerebral arterioles were prepared as described previously.1,6,13 Briefly, 41 brains were removed from male Sprague-Dawley rats (Harlan, Indianapolis, Ind), weighing 350 to 450 g, under pentobarbital sodium (65 mg/kg IP) anesthesia and placed into a refrigerated (4°C) dissection chamber filled with 3-(N-morpholino) propanesulfonic acid (MOPS)–buffered saline (in mmol/L: 144 NaCl, 3.0 KCl, 2.5 CaCl₂, 1.4 MgSO₄, 2.0 pyruvate, 5.0 glucose, 0.02 ethylenediaminetetraacetic acid, 1.21 NaH₂PO₄, and 2.0 MOPS). Vessels were isolated from the middle cerebral artery and transferred to an organ bath (2.5-mL volume) mounted on the stage of an inverted microscope (Diaphot; Nikon). The arteriole was cannulated on 1 side with a perfusion pipette and occluded with a collecting pipette. No intraluminal flow was given in all experiments. The passive internal diameter and length of the arteriole were determined after application of a transmural pressure of 60 mm Hg. The bath temperature was raised from room temperature to 37.5°C. The organ bath was continuously circulated with a peristaltic pump (model 203, Scientific Industries) at a rate of 0.5 mL/min. After an equilibration period, the arteriole constricted spontaneously (>20% decrease from the passive diameter) at a pH of 7.3. Only vessels responding to changes in pH (>15% decrease and increase from the control diameter from 7.3 to 7.65 and 6.8, respectively) were accepted for data analysis.

Vessel Diameter Measurements
The arteriole was observed with the use of a video system (CCD 72 and GenIIsys, Dage-MTI) and displayed on a video monitor. For measurement of the luminal diameter, a computerized diameter tracking system (Diamtrak software, Montech PTI) was used. The data were recorded and stored digitally (WinDaq, DataQ Instruments).

Vascular Response to Global [K⁺]
Dose responses of the arteriolar diameter to global [K⁺] were obtained from 3 (control concentration) to 30 mmol/L. [K⁺], was globally elevated in the organ bath by replacing the control buffer with isotonic K⁺ MOPS-buffered saline, which was prepared by substituting NaCl with an equimolar amount of KCl. To assess the mechanism of global [K⁺]–induced responses, we used 10 μmol/L ouabain (Na⁻/K⁺-ATPase inhibitor)16 and/or 4 K⁺ channel inhibitor8,17,19; 1 mmol/L tetaethylammonium ion (TEA) (calcium-activated K⁺ channel inhibitor); 3 μmol/L glibenclamide (ATP-sensitive K⁺ [Kₐ₃₆₃] channel inhibitor); 0.1 mmol/L 4-aminopyridine (4-AP) (voltage-dependent K⁺ channel inhibitor); and 30 μmol/L BaCl₂ (K⁺ channel inhibitor). We previously confirmed that these concentrations of K⁺ channel inhibitors were sufficient and specific.19 All inhibitors were applied extraluminally.

Vascular Response to Local [K⁺]
Local vasomotor stimuli with KCl (0.5 mol/L dissolved in distilled water) were applied through boron silicate glass micropipettes (TW100F-6, World Precision Instruments) pulled (model P-87, Sutter Instrument) to a tip (1.5- to 2.0-μm inner diameter). The micropipettes were backfilled with filtered solution and positioned in close proximity to the arteriolar wall. KC1 was applied by a pressure ejection system (50 to 450 ms in 100-ms steps at 20 psi with the use of 100% nitrogen gas) to obtain a dose response at the site of stimulation (local). Then the micropipette was moved to the opposite (remote) site of the vessel, and the same stimulation was used to observe conducted responses. Previously, we demonstrated that control ejections had no effect on the vessel diameter and that conducted vasomotor responses traveled equally up or down the vessel.1 Local and conducted responses were studied before and after the following treatments: (1) extraluminal 10 μmol/L ouabain; (2) extraluminal and intraluminal 30 μmol/L BaCl₂; (3) extraluminal 1 mmol/L TEA, 3 μmol/L glibenclamide, and 100 μmol/L 4-AP; (4) extraluminal 10 μmol/L Nω-nomethyl-L-arginine (L-NMMA) as nitric oxide (NO) synthase inhibitor and extraluminal 10 μmol/L indomethacin as cyclooxygenase inhibitor; and (5) endothelial impairment. The endothelium was removed by passing air through the lumen of the arteriole. This method has been described in detail previously.20 In our preparation with intact endothelium, extraluminally applied acetylcholine does not dilate the arteriole.15 Thus, endothelial but not smooth muscle cell damage was confirmed with extraluminal propidium iodide after air embolism.20 We also applied sodium nitroprusside to determine the functional vasodilator ability of the vessels before and after the endothelial damage. After air embolization, impairment of the endothelium was further confirmed with the use of extraluminal uridine triphosphate (UTP), a purinocceptor agonist that requires an intact endothelium for dilation.20

Measurement of Microapplied Apparent Potassium Concentration
A potassium-sensitive mini-electrode (WPI) was calibrated according to manufacturer’s instructions (sensitivity of 6.6 mV per mmol/L potassium, attached to Microsensor II, Diamond) and mounted in the microscope chamber. Similar to our experiments, a micropipette filled with 0.5 mol/L potassium was advanced to the ion-sensitive electrode membrane until a maximal signal to 450-ms pulses was obtained. The time course of the potassium application was recorded digitally (WinDaq, DataQ Instruments).

Drugs and Statistical Analysis
All drugs were purchased from Sigma. Only 1 vessel was used from each animal. Experimental values represent mean ± SEM; n indicates the number of vessels studied. Significant differences (P<0.05) were determined by ANOVA with a post hoc Student-Newman-Keuls test and paired Student’s t test, as appropriate.

Results
All vessels (n=41) developed spontaneous tone to 36.5±1.4 μm (66.3±1.2% of their passive diameter). Acidosis (pH 6.8) dilated them to 126.9±1.2%, and alkalosis (pH 7.65) constricted them to 72.1±0.9%.

Vascular Response to Global [K⁺]
The global [K⁺], induced significant dilation of the vessel (n=7; Figure 1). The maximum dilation was 57.9±5.9% at...
15 mmol/L. \([K^+]_o\) ranging from 5 to 20 mmol/L produced sustained dilation (>5 minutes). In contrast, 30 mmol/L \([K^+]_o\) produced transient dilation (shown in Figure 1). Prolonged exposure constricted the vessel (mean, −15.1%).

Effect of Ouabain and \(K^+\) Channel Inhibitors on Global \([K^+]_o\)-Induced Dilation

We investigated global \([K^+]_o\) at 5 mmol/L \([K^+]_o\) in the presence or absence of inhibitors. Ouabain transiently elicited constriction, but the vessels returned to the control diameter within 15 minutes (Table). The global \([K^+]_o\)-induced dilation was significantly attenuated by ouabain (Figure 2; n=5). BaCl_2 (30 mmol/L) constricted the arteriolar diameter (Table) but did not affect dilation to global \([K^+]_o\) (Figure 2; n=5). In preliminary experiments, there were also no inhibitory effects of 100 μmol/L barium alone or 30 μmol/L barium in the presence of ouabain. The global \([K^+]_o\)-mediated dilation was not inhibited by combined treatment with 1 mmol/L TEA, 3 μmol/L glibenclamide, and 100 μmol/L 4-AP (32.0±5.2% versus 45.0±11.5%; n=4).

Vascular Responses to Local \([K^+]_o\)

Vessels had a length of 1142±68 μm (n=26). Figure 3 shows the data for microejection of KCl causing initial constriction followed by secondary dilation at the site of stimulation (local), which traveled along the vessel (conducted). Secondary dilation was consistently conducted at all pulse durations, while initial constriction needed longer pulse durations to be significant. Maximum initial local constriction was −5.7±1.3%, and secondary dilation was 30.4±2.4% for 450-ms pulse. At the remote stimulation, peak conducted initial constriction occurred rapidly (∼1 second) and was −3.7±1.2%, and secondary dilation was 27.3±2.5% for 450-ms pulse. These data indicate that local \([K^+]_o\)-induced conducted responses attenuated very little. Local secondary dilations observed at the highest pulse of 450 ms correspond to those achieved by global \([K^+]_o\), from 3 (control) to 5 mmol/L (36.8±9.1%) (Figures 1 and 3). Figure 3C shows the pulse-concentration relationship for microapplied potassium. The apparent potassium concentration increases linearly and reaches a maximum of 4.3 mmol/L potassium for 1 second (Figure 3C).

Effect of Ouabain and \(K^+\) Channel Inhibitors on Local \([K^+]_o\)-Induced Responses

Ouabain depressed both the local and conducted dilations to local \([K^+]_o\), but had no effect on constrictor responses (Figure 4; n=5). Additional treatment of extraluminal BaCl_2 (30 μmol/L) did not produce further inhibition of local dilation (n=3; data not shown). In a separate series, effects of extraluminal and intraluminal BaCl_2 were examined. Extraluminal 30 μmol/L BaCl_2 decreased the control diameter (Table), while intraluminal 30 μmol/L BaCl_2 had no effect on the control diameter (Table). Extraluminally applied BaCl_2 impaired conducted but not local constriction and dilation (Figure 5A; n=5). In contrast, intraluminal BaCl_2 caused no significant effect on local or conducted responses (Figure 5B; n=4). Extraluminal 0.1 mmol/L 4-AP had no effect on local and conducted responses (Figure 6; n=4). 4-AP itself caused significant constriction of arterioles (Table). Additional treatment of 1 mmol/L TEA and 3 μmol/L glibenclamide also did not change local and conducted responses (Figure 6; n=4).

Effect of NO Synthase and Cyclooxygenase Products on Local \([K^+]_o\)-Induced Responses

Extraluminal 10 μmol/L L-NMMA induced a significant vasoconstriction (Table). The local \([K^+]_o\)-evoked local and conducted responses were not changed in the presence of L-NMMA (n=4; data not shown). Subsequent treatment of 10 μmol/L indomethacin with L-NMMA also had no effect on these responses (n=4; data not shown).

### Table: Arteriolar Diameter Before and After Administration of Inhibitors or Air Embolism

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>n</th>
<th>Before, μm</th>
<th>After, μm</th>
<th>% of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain (10 μmol/L)</td>
<td>10</td>
<td>35.5±3.8</td>
<td>36.1±4.0</td>
<td>1.5±1.1</td>
</tr>
<tr>
<td>BaCl_2 (extraluminal 30 μmol/L)</td>
<td>10</td>
<td>36.7±2.5</td>
<td>34.3±2.5</td>
<td>−6.8±1.5*</td>
</tr>
<tr>
<td>BaCl_2 (intraluminal 30 μmol/L)</td>
<td>4</td>
<td>35.9±5.6</td>
<td>35.0±5.1</td>
<td>−2.1±0.9</td>
</tr>
<tr>
<td>4-AP (100 μmol/L)</td>
<td>4</td>
<td>40.5±6.8</td>
<td>36.0±8.0</td>
<td>−13.1±4.8*</td>
</tr>
<tr>
<td>L-NMMA (10 μmol/L)</td>
<td>4</td>
<td>40.4±2.7</td>
<td>29.9±2.9</td>
<td>−26.4±2.4*</td>
</tr>
<tr>
<td>Air emboli</td>
<td>4</td>
<td>38.9±1.3</td>
<td>37.0±1.4</td>
<td>−4.8±1.3*</td>
</tr>
</tbody>
</table>

*Values are mean±SEM; n is number of observations.

*Significant differences (P<0.05) from control.
Effect of Endothelial Impairment on Local $[K^+]_o$-Induced Responses

The disruption of the endothelium by air emboli significantly constricted the vessel (Table). The dilation in response to 100 nmol/L sodium nitroprusside ($12.8 \pm 1.9\%$ [before air embolization] versus $15.1 \pm 3.3\%$ [after air embolization]) was not altered by air embolization ($n=4$). We also confirmed that air embolization abolished 1 pmol/L UTP-induced dilation ($1.4 \pm 1.0\%$), which depends on an intact endothelium. Additional treatment of 10 µmol/L ouabain inhibited both local and conducted dilation ($n=4$).

Discussion

Response to Global $[K^+]_o$ and Na$^+$-$K^+$-ATPase

It is well known that small elevations of $[K^+]_o$ cause dilation of cerebral vessels via stimulation of $K_{IR}$ channels and/or Na$^+$-$K^+$-ATPase. The sodium pump is electrogenic (3 Na out for 2 K in per cycle), and stimulation of the pump activity will produce hyperpolarization and relaxation of vascular smooth muscle. The other mechanism of global $[K^+]_o$-induced dilation is the activation of smooth muscle $K_{IR}$ channels, resulting in hyperpolarization. Recently, Zaritsky et al. proposed that $K_{IR}$ was the sole mediator of global $[K^+]_o$-mediated dilation in mice.
McCarron and Halpern\textsuperscript{13} demonstrated that the activity of 2 independent mediators depended on \( [K^+]_o \). Thus, a small increase in \( [K^+]_o \) up to 5 mmol/L stimulated \( Na^+-K^+-\text{ATPase} \), whereas higher \( [K^+]_o \) (7 to 15 mmol/L) mainly activated \( K_{IR} \) channels. In our study global \( [K^+]_o \)-mediated dilation from 3 to 5 mmol/L was significantly attenuated by ouabain but not \( K^+ \) channel inhibitors, including \( \text{BaCl}_2 \). We have previously shown that 30 \( \mu \text{mol/L} \) \( \text{BaCl}_2 \) is sufficient to block \( K_{IR} \) channels in our model.\textsuperscript{19} Thus, small global \( [K^+]_o \) increases (3 to 5 mmol/L) stimulate the smooth muscle \( Na^+-K^+-\text{ATPase} \) but not \( K^+ \) channels, including \( K_{IR} \) channels in rat cerebral arterioles. It is possible that higher \( [K^+]_o >5 \) mmol/L can stimulate \( K_{IR} \) channels in our preparation.

In rat penetrating arterioles perfused at 4 \( \mu \text{L/min} \), it was found that \( K_{ATP} \) channels mediate potassium-induced arteriolar dilation.\textsuperscript{8} Although our study used higher concentrations of glibenclamide (3 \( \mu \text{mol/L} \)) to inhibit \( K_{ATP} \), we found no effect on potassium-induced vessel dilation. Because we found earlier\textsuperscript{1} that 3 \( \mu \text{L/min} \) perfusion affected ATP-induced conducted responses, we performed our experiments without intraluminal perfusion. The mechanism by which intraluminal perfusion may unmask \( K_{ATP} \) activity needs further study.

Response to Local \( [K^+]_o \)

Microapplication (3 to 5 mmol/L) of KCl produced a transient constriction followed by dilation, and these responses were conducted along the cerebral arteriole. Hungerford et al\textsuperscript{23} reported that microejection of KCl mediated a similar biphasic response in arterioles of the mouse cremaster muscle. Thus, local \( [K^+]_o \)-induced conducted responses appear to control the regional blood flow and to be coordinated within and among vascular trees.

Local \( [K^+]_o \)-Induced Constriction

The local \( [K^+]_o \) resulted in a small transient constriction (\(-5.7\%\); Figure 3). We previously reported that such a potassium-induced constriction corresponds to a membrane depolarization of 2.4 mV.\textsuperscript{24} The Nernst equation predicts a small depolarization of 3.7 mV when extraluminal potassium is raised to 4.3 mmol/L. As such, the observed transient constriction to local \( [K^+]_o \), may be induced by the depolarizing effect on smooth muscle cells through the Nernst effect,\textsuperscript{23,25} which is then superseded by a secondary mechanism such as hyperpolarizing \( Na^+-K^+-\text{ATPase} \) activation.

Local \( [K^+]_o \)-Induced Dilation

The local \( [K^+]_o \) (3 to 5 mmol/L) stimulated a secondary dilation that was blocked by ouabain but not \( \text{BaCl}_2 \). These results are the same as with global \( [K^+]_o \). In addition, ouabain also inhibited conducted dilation. Thus, the activation of smooth muscle \( Na^+-K^+-\text{ATPase} \) seems to be the generator for conducted dilation to local \( [K^+]_o \). To our knowledge, this is the first report that \( Na^+-K^+-\text{ATPase} \) activation can act as the generator for conducted vasodilation.

The local \( [K^+]_o \)-mediated dilation may be endothelium independent.\textsuperscript{14,21} Neither endothelial impairment nor NO synthase inhibition affected local \( [K^+]_o \)-evoked local responses, consistent with previous studies.\textsuperscript{14,21} Thus, it is unlikely that the endothelium and NO played an important role in the local responses to local \( [K^+]_o \). By contrast, Dreier et al\textsuperscript{26} reported that global \( [K^+]_o \), induced elevation of cerebral blood flow, which was attenuated by NO synthase inhibitor in closed cranial window experiments. However, they did not address the source of NO. It is therefore possible that neuronal NO can modulate the vasodilator responses to global \( [K^+]_o \).

We did not find any effect of indomethacin on local responses to local \( [K^+]_o \), suggesting that these responses are independent of cyclooxygenase products such as prostaglandins.

Role of Endothelium and Smooth Muscle in Conduction

Local \( [K^+]_o \) consistently resulted in conducted vasodilation, whereas a significant conducted constriction was observed only at high pulses. Previously we reported the similar conducted response mediated by ATP in rat cerebral arterioles.\textsuperscript{1} ATP stimulation caused biphasic responses locally, but only the secondary dilation was conducted. We\textsuperscript{1} and others\textsuperscript{27} speculated that the endothelial rather than smooth muscle layer acts as the conduction pathway. Recent studies found that both cell layers (endothelium, smooth muscle cell,
or both) may serve as the conduction pathway. Emerson and Segal clearly demonstrated that acetylcholine-evoked conducted dilation traveled via endothelial but not smooth muscle cell in isolated, cannulated feed arteries of the hamster retractor muscle. In contrast, the dilation to acetylcholine was conducted through both layers of hamster cheek pouch arterioles in vitro. Additionally, the smooth muscle cell was the generator of phenylephrine-mediated constriction and pathway for conduction. These observations strongly suggest that conduction pathways are dependent on agonists and location of the vessel. In the present study local \([K^+]_o\)-induced depolarization and hyperpolarization generated in the smooth muscle are electrically propagated through myoendothelial gap junctions to the endothelial cell and that hyperpolarization after depolarization travels through the endothelial but not smooth muscle layer. Then endothelial depolarization followed by hyperpolarization is transmitted to vascular smooth muscle at a remote site, resulting in conducted constriction followed by dilation in rat cerebral penetrating arterioles. We cannot exclude the possibility that the smooth muscle cell also plays a role in regulation of conduction because the endothelial impairment did not abolish conducted responses. However, air embolization does not completely remove the endothelium in microvessels. Hence, some of the remaining conduction could be attributed to the physical presence of the endothelium as an electric conductor. Further studies are needed to substantiate the role for gap junctions in conducted vasomotor responses in rat cerebral arterioles.

Neither NO nor prostaglandins are essential to local \([K^+]_o\)-induced conduction, consistent with previous studies.
Role of Endothelial and Smooth Muscle K IR Channels in Conduction

K IR channels are expressed in both vascular endothelial and smooth muscle cells. However, the expression of this channel varies greatly between endothelial and smooth muscle cells. Although K IR channels are mainly expressed in smooth muscle of microvessels and endothelium of macrovessels, the functional difference of this variability is unknown. In the microcirculation, smooth muscle K IR channels may contribute to maintaining the resting membrane potential. In our preparation K IR channels also regulated the vascular tone under resting conditions. A recent study suggested that extraluminal barium is impermeable to the blood-brain barrier in cerebral penetrating arteriole. In the present study extraluminal but not intraluminal 30 mmol/L BaCl 2 attenuated the conducted but not local responses. These data suggest that smooth muscle rather than endothelial K IR channel activity may be the underlying mechanism for sustaining conducted response to local [K+]o. This contribution may be explained by 2 hypotheses: (1) smooth muscle K IR channel may maintain hyperpolarization caused by local [K+]o and Na+-K+-ATPase activation, and (2) smooth muscle K IR channels activity may be related to the function and/or conductance of myoendothelial gap junctions. Lin and Duling suggested that an appropriate vascular tone is necessary to produce the conducted response. In addition, the conduction is sensitive to membrane potential. We propose that the resting vascular tone maintained by smooth muscle K IR channels may be an important contributor of local [K+]o-mediated conduction in rat cerebral arterioles. However, we cannot exclude the possibility that an unknown barium-sensitive factor contributes to myoendothelial gap junctional regulation. In the cerebral microcirculation, it would seem that smooth muscle K IR channels act as a sustainer but not a generator for the response to local [K+]o-mediated conduction. This seems to favor the conducted dilation over the conducted constriction because the constriction was not enhanced in the presence of barium.

Pathophysiological Consequences

On the basis of this study, local [K+]o-mediated conduction is maintained by intact endothelium, smooth muscle Na+-K+-
ATPase, and $K_{ir}$ channel under physiological conditions. Endothelial dysfunction produced by, for example, oxyhemoglobin after subarachnoid hemorrhage would greatly attenuate the conducted responses and thus diminish the ability of the microcirculation to regulate local blood flow. In addition, other pathological conditions such as hypertension and ischemia/reperfusion can impair elevated $[K^+]_o$-mediated dilation, including conduction.

In conclusion, a small increase in $[K^+]_o$ is a powerful agonist inducing conducted responses in rat cerebral penetrating arterioles. The local dilation to elevated $[K^+]_o$ (3 to 5 mmol/L) is mediated by the stimulation of Na$^+$-$K^+$-ATPase but not $K_{ir}$ channels. The local responses to elevated $[K^+]_o$ may spread along the endothelial cell layer rather than smooth muscle cell. Smooth muscle $K_{ir}$ channels may regulate the conducted dilation induced by elevated $[K^+]_o$.

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References
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