Cerebral Blood Flow During Hemodilution and Hypoxia in Rats

Role of ATP-Sensitive Potassium Channels

Yoshinobu Tomiyama, MD; Johnny E. Brian, Jr, MD; Michael M. Todd, MD

Background and Purpose—Hypoxia and hemodilution both reduce arterial oxygen content (CaO₂) and increase cerebral blood flow (CBF), but the mechanisms by which hemodilution increases CBF are largely unknown. ATP-sensitive potassium (Kₘₐₜₚ) channels are activated by intravascular hypoxia, and contribute to hypoxia-mediated cerebrovasodilatation. Although CaO₂ can be reduced to equal levels by hypoxia or hemodilution, intravascular PO₂ is reduced only during hypoxia. We therefore tested the hypothesis that Kₘₐₜₚ channels would be unlikely to contribute to cerebrovasodilatation during hemodilution.

Methods—Glibenclamide (19.8 μg) or vehicle was injected into the cisterna magna of barbiturate-anesthetized rats. The dose of glibenclamide was chosen to yield an estimated CSF concentration of 10⁻⁴ M. Thirty minutes later, some animals underwent either progressive isovolumic hemodilution or hypoxia (over 30 minutes) to achieve a CaO₂ of ≈7.5 mL O₂/dL. Other animals did not undergo hypoxia or hemodilution and served as controls. Six groups of animals were studied: control/vehicle (n = 4), control/glibenclamide (n = 4), hemodilution/vehicle (n = 10), hemodilution/glibenclamide (n = 10), hypoxia/vehicle (n = 10), and hypoxia/glibenclamide (n = 10). CBF was then measured with ³H-nicotine in the forebrain, cerebellum, and brain stem.

Results—In control/vehicle rats, CBF ranged from 72 mL · 100 g⁻¹ · min⁻¹ in forebrain to 88 mL · 100 g⁻¹ · min⁻¹ in the brain stem. Glibenclamide treatment of control animals did not influence CBF in any brain area. Hemodilution increased CBF in all brain areas, with flows ranging from 128 mL · 100 g⁻¹ · min⁻¹ in forebrain to 169 mL · 100 g⁻¹ · min⁻¹ in the brain stem. Glibenclamide treatment of hemodiluted animals did not affect CBF in any brain area. Hypoxia resulted in a greater CBF than did hemodilution, ranging from 172 mL · 100 g⁻¹ · min⁻¹ in forebrain to 259 mL · 100 g⁻¹ · min⁻¹ in the brain stem. Glibenclamide treatment of hypoxic animals significantly reduced CBF in all brain areas (P < 0.05).

Conclusions—Both hypoxia and hemodilution increased CBF. Glibenclamide treatment significantly attenuated the CBF increase during hypoxia but not after hemodilution. This finding supports our hypothesis that Kₘₐₜₚ channels do not contribute to increasing CBF during hemodilution. Because intravascular PO₂ is normal during hemodilution, this finding supports the hypothesis that intravascular PO₂ is an important regulator of cerebral vascular tone and exerts its effect in part by activation of Kₘₐₜₚ channels in the cerebral circulation. (Stroke. 1999;30:1942-1948.)

Key Words: cerebral blood flow ■ hemodilution ■ hypoxia ■ potassium channels ■ vasodilation ■ rats
these differences may affect mechanisms of vasodilatation. One important difference is intravascular PO$_2$. The arterial partial pressure of oxygen (PaO$_2$) is normal during hemodilution but is reduced during hypoxia. Because $K_{ATP}$ channels appear to be activated by a reduction in intravascular PO$_2$ and $K_{ATP}$ channels contribute to cerebrovasodilatation during hypoxia, intravascular PO$_2$ appears to be an important independent regulator of cerebral vascular tone and CBF. We hypothesized that activation of cerebral vascular $K_{ATP}$ channels would be unlikely after hemodilution because intravascular PO$_2$ is normal, and that blockade of $K_{ATP}$ would not reduce CBF following hemodilution.

**Materials and Methods**

**Animal Preparation**

All experiments were approved by the University of Iowa Animal Care and Use Committee. Forty-eight male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Ind) weighing 310 to 400 g were anesthetized with 4% to 5% halothane in 100% oxygen in a plastic box. When anesthetized, the animal was removed from the box and 1% lidocaine infiltrated subcutaneously into the anterior neck. A tracheotomy was performed and the animal ventilated with a tidal volume of 10 mL/Kg at the rate of 40 to 50 breaths/min, using an inspired gas mixture of 1.0% halothane in 40% O$_2$/balance N$_2$. Ventilator rate was adjusted to achieve normocarbia. Skeletal muscle paralysis was produced with pancuronium bromide (0.25 mg/kg). Both groin areas were infiltrated with 1% lidocaine, and bilateral femoral arterial and venous catheters (PE-50) were inserted. Mean arterial pressure (MAP) was continuously measured from the left femoral artery (model 79 polygraph, Grass Medical Instrument). Arterial blood was intermittently sampled for determination of pH and arterial blood gases (Instrumentation Laboratory System 1306) as well as Ca$_O_2$ (Radiometer OM3, calibrated for rat blood). Hematocrit was determined by microcapillary tube centrifugation. Rectal temperature was maintained at 37°C to 38°C with a heating pad.

After preparation (approximately 45 minutes), the halothane was discontinued and animals loaded with pentobarbital (50 mg/kg), followed by a maintenance infusion (18 mg·kg$^{-1}$·hr$^{-1}$). Animals were turned prone and the head fixed in a stereotactic frame. The posterior occipital area was infiltrated with 1% lidocaine, and the atlantooccipital membrane was exposed through a midline incision. A 27 gauge needle was inserted into the cerebellomedullary cistern and cyanoacrylate glue was applied around the needle to prevent cerebrospinal fluid (CSF) leakage.

**Drug Preparation and Administration**

Glibenclamide (Sigma Chemical Co) was dissolved in dimethyl sulfoxide (DMSO) and then diluted in artificial CSF (pH 7.25 to 7.33, PCO$_2$ 40 to 45 mm Hg, PO$_2$ 40 to 80 mm Hg) to a final concentration of 4×10$^{-4}$ M. One hundred microliters of CSF was slowly removed from the cerebellomedullary cistern by aspiration, and 100 μL of the glibenclamide solution was injected over 10 minutes. Assuming a rat CSF volume of 400 μL, the final in vivo concentrations of glibenclamide is $\approx 10^{-4}$ M (ie, a 1:4 dilution of the stock solution) and DMSO is 0.825%. An identical solution without glibenclamide was injected in vehicle groups.

**Experimental Protocols**

To investigate the effect of glibenclamide on basal CBF, rats were randomly assigned to 2 groups: (1) control with intracisternal injection of vehicle (control/vehicle, n=4) and (2) control with intracisternal injection of glibenclamide (control/glibenclamide, n=4). Additional rats were then randomly assigned to 4 groups: (3) hemodilution with intracisternal injection of vehicle (hemodilution/vehicle, n=10), (4) hemodilution with intracisternal injection of glibenclamide (hemodilution/glibenclamide, n=10), (5) hypoxia with intracisternal injection of vehicle (hypoxia/vehicle, n=10), and (6) hypoxia with intracisternal injection of glibenclamide (hypoxia/glibenclamide, n=10).

After the intracisternal injection of glibenclamide or vehicle, animals remained undisturbed for 30 minutes. In the hemodilution groups, a stepwise isovolumic hemodilution was then performed. Arterial blood was removed and replaced with an approximately equal volume of warmed 6% hetastarch in saline (Hespan, DuPont Critical Care) until a target CaO$_2$ of $\approx 7.5$ mL O$_2$/dl was reached. This process took approximately 30 minutes. MAP was controlled at 120 mm Hg by the continuous infusion of methoxamine hydrochloride (Burroughs Wellcome Co). In the hypoxic groups, a stepwise hypoxemia was achieved by incremental reductions in FiO$_2$ (produced by changing the O$_2$/N$_2$ ratio) until a target CaO$_2$ of $\approx 7.5$ mL O$_2$/dl was reached. As with hemodilution, this process took place over approximately 30 minutes, and methoxamine was used to maintain MAP.

In the control groups, anesthesia and ventilation were continued as above, with no alternations in PaO$_2$ and CaO$_2$. When target CaO$_2$ values had been reached in the 4 intervention groups (or at an equivalent time point in controls), 10 μCi of $^3$H-nicotine (20 mg; New England Nuclear) diluted in 0.6 to 0.7 mL of saline was infused intravenously at a calibrated rate of 0.726 mL/min for 40 seconds. Blood was simultaneously withdrawn at the same rate from the right femoral artery into a heparinized syringe. At the end of the 40 seconds, the pump was shut off, KCl was injected intravenously, and both infusion and withdrawal lines were immediately clamped.

**Sample Processing**

**Brain**

The brain was quickly removed from the skull and separated from the dura and sagittal sinus. The forebrain, cerebellum, and brain stem were separated and divided. Each sample was weighed, placed in a scintillation vial, and 2 mL of TS-2 tissue solubilizer (Research Products International) was added. The vials were placed in a oven at 50°C for 24 hours. The contents of each vial were neutralized by adding 70 μL of glacial acetic acid. Each sample was then suspended in 16 mL of 3a20 scintillation cocktail (Research Products International Corp).

**Blood/Plasma**

Blood remaining in the tubing was drawn into the syringe with 0.3 mL of water. $^3$H activity was determined in three 50-μL aliquots of blood from the withdrawal syringe. Each aliquot was placed in a scintillation vial and solubilized in 1 mL TS-2 at 50°C for 30 minutes. The blood samples were decolorized with 200 μL benzoyl peroxide (0.2 g/mL in toluene) at 50°C for an additional 30 minutes. Blood samples were neutralized with 35 μL glacial acetic acid. Each sample was then suspended in 16 mL of 3a20 scintillation cocktail (Research Products International Corp).

**Calculations**

Regional blood flow (in mL·100 g$^{-1}$·min$^{-1}$) was calculated by the indicator fractionation method$^{10,11}$:

$$\text{CBF} = \frac{\text{Syringe flow} \times \text{Tissue dpm}}{\text{Syringe dpm}} \frac{\text{Syringe dpm}}{\text{Tissue weight}}$$

Reference syringe flow was 0.726 mL/min.

**Statistics**

Data were analyzed by an ANOVA with a Duncan’s post hoc test. $P<0.05$ was accepted as significant. Results are expressed as mean±SD.
Results

Systemic Variables

Systemic variables are shown in Table 1. As intended, hematocrit, PaO₂, and CaO₂ differed between groups. Hypoxia and hemodilution reduced CaO₂ to equivalent levels. There were no differences in MAP, PaCO₂, pH, or temperature between groups. Plasma glucose concentration was increased in both the hemodilution and hypoxia vehicle groups compared with controls. Intracisternal administration of glibenclamide significantly decreased blood glucose concentration in all 3 glibenclamide-treated groups. A greater rate of methoxamine infusion was required in hypoxic animals compared with hemodiluted animals.

Regional Blood Flow

Regional CBF values are shown in Table 2. In control animals treated with calcium, blood flows were similar to values previously reported and ranged from 72±14 mL·100 g⁻¹·min⁻¹ in the forebrain to 88±16 mL·100 g⁻¹·min⁻¹ in the brain stem. During hypoxia, blood flow was increased by hemodilution and hypoxia (Table 2; P<0.05). Following hemodilution, blood flow was 128±12 mL·100 g⁻¹·min⁻¹ in the forebrain and 169±17 mL·100 g⁻¹·min⁻¹ in the brain stem. Regional cerebral blood flows during hypoxia were greater in all areas than during hemodilution, and averaged 172±27 mL·100 g⁻¹·min⁻¹ in the brain stem (P<0.05). Intracisternal glibenclamide significantly attenuated the increase of the blood flow in forebrain, cerebellum and brain stem during hypoxia (P<0.05). However, glibenclamide did not significantly reduce CBF after hemodilution.

Discussion

In our study, CaO₂ was reduced to equal levels by hypoxia and hemodilution, but PaO₂ values were markedly different between the two conditions. Blockade of KATP channels only affected CBF when PaO₂ was reduced. The findings suggest that factors other than CaO₂ play a role in controlling CBF during hypoxia and hemodilution and suggest that PaO₂ may directly regulate cerebral vascular tone. Our findings are consistent with the hypothesis that reduced intravascular Po₂ during hypoxia, but not hemodilution, leads to activation of KATP channels and increased CBF. Our findings are also consistent with a previous investigation in isolated rat

### Table 1. Systemic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Hemodilution</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (n=4)</td>
<td>Gibenclamide (n=4)</td>
<td>Vehicle (n=10)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41±1</td>
<td>41±1</td>
<td>15±1</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>164±10</td>
<td>165±24</td>
<td>172±7</td>
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<tr>
<td>CaO₂, mL·100 g⁻¹·dL⁻¹</td>
<td>19.0±0.3</td>
<td>19.2±0.5</td>
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<tr>
<td>pH</td>
<td>7.45±0.01</td>
<td>7.44±0.02</td>
<td>7.42±0.02</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>40±2</td>
<td>39±1</td>
<td>39±3</td>
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<tr>
<td>MAP, mm Hg</td>
<td>124±11</td>
<td>125±13</td>
<td>118±8</td>
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<tr>
<td>Temperature, °C</td>
<td>38.0±0.0</td>
<td>38.0±0.1</td>
<td>38.0±0.2</td>
</tr>
<tr>
<td>Glucose, mg·dL⁻¹</td>
<td>133±44</td>
<td>91±13*</td>
<td>207±25†</td>
</tr>
<tr>
<td>Methoxamine, mg·hr⁻¹</td>
<td>0</td>
<td>0</td>
<td>0.18±0.32</td>
</tr>
</tbody>
</table>

Values are mean±SD. PaO₂ and PaCO₂, arterial partial pressure of O₂ and CO₂, respectively; CaO₂, arterial O₂ content; and methoxamine, final methoxamine infusion rate.

*P<0.05 compared with respective vehicle group; †P<0.05 compared with control group; ‡P<0.05 compared with respective hemodilution/vehicle group.

### Table 2. Regional Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Hemodilution</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (n=4)</td>
<td>Gibenclamide (n=4)</td>
<td>Vehicle (n=10)</td>
</tr>
<tr>
<td>Forebrain, mL·100 g⁻¹·min⁻¹</td>
<td>72±14</td>
<td>70±6</td>
<td>128±12†</td>
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<tr>
<td>Cerebellum, mL·100 g⁻¹·min⁻¹</td>
<td>86±19</td>
<td>81±7</td>
<td>169±24†</td>
</tr>
<tr>
<td>Brain stem, mL·100 g⁻¹·min⁻¹</td>
<td>88±16</td>
<td>85±11</td>
<td>169±17†</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 compared with respective vehicle group; †P<0.05 compared with control/vehicle group; ‡P<0.05 compared with hemodilution/vehicle group.
middle cerebral arteries, in which intraluminal but not extravascular hypoxia resulted in vasodilatation that could be attenuated by blockade of K<sub>ATP</sub> channels. Overall, these data suggest that intravascular P<sub>O2</sub> is an important independent regulator of cerebral vascular tone and controls CBF in part by activation of K<sub>ATP</sub> channels.

In the present study, we observed that hypoxia resulted in a greater increase in CBF, which is consistent with prior reports from our laboratory. This finding supports the concept that some control mechanisms differ between hypoxia and hemodilution. The present results suggest that activation of K<sub>ATP</sub> channels is one vascular control mechanism that contributes to a greater CBF during hypoxia.

Under control conditions, intracisternal injection of glibenclamide did not affect CBF. Potassium channels in vascular smooth muscle regulate smooth muscle tone by regulation of membrane potential. When potassium channels are active (open), vascular smooth muscle hypoperforates and relaxes. For glibenclamide to affect vascular smooth muscle tone, K<sub>ATP</sub> channels must be in the open state. Glibenclamide did not reduce CBF under normal conditions, which indicates that K<sub>ATP</sub> channels are not active and do not contribute to basal regulation of cerebrovascular tone. This finding is consistent with prior studies which report that blockade of K<sub>ATP</sub> channels under baseline conditions does not alter cerebral vascular tone or hypoperforate cerebrovascular smooth muscle.

Hypoxia and hemodilution also differ in the reduction in whole-blood viscosity that occurs after hemodilution, which could independently influence CBF. Blood viscosity can influence blood flow by both active and passive mechanisms. In abdominal aorta, endothelial release of NO is increased as viscosity is increased, and the viscosity-mediated increase in NO release can be attenuated with glibenclamide. This suggests that increasing viscosity activates K<sub>ATP</sub> channels in vascular endothelial cells, resulting in NO release. Brain microvascular endothelial cells express K<sub>ATP</sub> channels, which could modulate brain endothelial NO release. However, based on this information, a reduction in whole-blood viscosity after hemodilution would be expected to reduce activity of endothelial K<sub>ATP</sub> channels and reduce endothelial release of NO. Thus, it would seem unlikely that endothelial cell K<sub>ATP</sub> channels could contribute to increased CBF following hemodilution. Consistent with this, we did not find a role for K<sub>ATP</sub> channels in modulating CBF when whole-blood viscosity was reduced after hemodilution. Furthermore, we have shown that there is no role for NO in regulation of CBF after hemodilution. We do not think that viscosity-related changes in endothelial cell K<sub>ATP</sub> activity and/or NO release contributed to the increase in CBF after hemodilution.

Reduced blood viscosity can also cause a passive increase in CBF after hemodilution. By reducing the resistance to flow, reduced blood viscosity increases cerebral blood flow without vasodilatation. We and others have previously reported that the reduction of blood viscosity after hemodilution is responsible for approximately 50% of the increase in CBF. However, after hemodilution, 50% increase in CBF cannot be accounted for by reduced viscosity, which suggests that active vasodilatation also contributes to increased flow. After hemodilution, cerebral blood volume increases, which can occur only when cerebral blood vessels dilate. Thus, it appears that after hemodilution, active vasodilatory mechanisms must contribute to the increase in flow. In the current study, blockade of K<sub>ATP</sub> channels had no effect on the increase in CBF after hemodilution. In a previous study, we reported that inhibition of NO synthase did not affect the increase in CBF after hemodilution. Thus, although we have previously shown that the increase in CBF after hemodilution is dependent on both the reduction in viscosity and the reduction in oxygen content, we have not identified active mechanisms that mediate the increase in flow.

Results similar to ours on the role of K<sub>ATP</sub> channels in hypoxic cerebrovasodilatation have been reported. In our study, the relative contribution of the K<sub>ATP</sub> channels to the increase of CBF during hypoxia ranges from 17% in the brain stem to 32% in the forebrain. Reid et al. reported that K<sub>ATP</sub> blockade attenuated the increase of cortical CBF during hypoxia by 66% to 67%. The difference between our findings and those of Reid et al may be related to control of blood pressure. Hypoxia causes hypotension in rats, and in the studies by Reid et al hypoxia reduced MAP by 30 to 40 mm Hg. Hypotension results in autoregulatory vasodilatation of cerebral blood vessels, which depends in part on activation of K<sub>ATP</sub> channels. Thus, hypotension during hypoxia could result in more marked activation of K<sub>ATP</sub> channels, and blockade of K<sub>ATP</sub> channels would produce a more marked reduction in CBF compared with hypoxia alone.

Limitations of the Current Study
In preliminary studies, we administered intravenous glibenclamide (20 to 30 mg/kg) to anesthetized rats, and tested efficacy of blockade by topically applying a K<sub>ATP</sub> agonist to cerebral arteries. Intravenous glibenclamide did not attenuate dilatation of cerebral arteries caused by topical K<sub>ATP</sub> agonist (unpublished observations), suggesting that systemic glibenclamide does not significantly penetrate the blood-brain barrier. In the present study, we therefore administered glibenclamide by intracisternal injection. We estimated the concentration of glibenclamide in CSF to be \( \approx 10^{-4} \) M, based on the dose of glibenclamide administered and the volume of CSF in rats. It is very likely that the final in vivo concentration was less than \( 10^{-4} \) M due to uptake into brain. After intracisternal administration of glibenclamide, plasma glucose was significantly reduced, which indicates that there was also systemic uptake of glibenclamide. Nevertheless, plasma glucose remained above levels associated with hypoglycemia-mediated increase in CBF. Because of diffusion of glibenclamide into brain and systemic uptake, we might not have achieved maximal blockade of K<sub>ATP</sub> channels in brain. However, 50 to 150 nmol/L glibenclamide induces half-maximal inhibition of K<sub>ATP</sub> activation in arterial preparations, and 1 \( \mu \)mol/L glibenclamide produces maximal inhibition of K<sub>ATP</sub> activation in cerebral arteries and arterioles. Our target concentration of glibenclamide in CSF was \( 10^{-4} \) M, 2 orders of magnitude greater than that required for maximal blockade of K<sub>ATP</sub> channels in cerebral arteries. However, because we did not test the efficacy of K<sub>ATP</sub> blockade in our preparations, we may have underestimated the role of K<sub>ATP</sub> channels in hypoxia-mediated cerebrovasodilatation.
We think that the attenuation of CBF during hypoxia by glibenclamide was due to blockade of K<sub>ATP</sub> channels and not due to nonspecific effects of glibenclamide. Most evidence suggests that glibenclamide is specific for inhibition of K<sub>ATP</sub> channels and does not affect activity of calcium-dependent (K<sub>Ca</sub>), inward rectifier (K<sub>IR</sub>), or voltage-dependent potassium channels. Furthermore, we do not think that glibenclamide exerted its effect via blockade of either K<sub>Ca</sub> or K<sub>IR</sub> channels, because both of these channels contribute to a baseline vasodilator tone in the cerebral circulation. Thus, blockade of K<sub>Ca</sub> or K<sub>IR</sub> channels under control conditions results in cerebrovasoconstriction. Our failure to see any effect of glibenclamide on baseline CBF suggests that neither channel was blocked by the concentration of glibenclamide we administered.

We used methoxamine, an alpha agonist, to maintain constant blood pressure during both hypoxia and hemodilution. We felt that this was necessary, as hypotension alone can activate K<sub>ATP</sub> channels in the cerebral circulation, which would complicate interpretation of our results. It is unlikely that intravenous infusion of methoxamine influenced CBF. Under normal conditions when the blood-brain barrier is intact, direct intracarotid infusion of alpha agonists do not alter CBF.

Nicotine can independently elevate CBF. However, as opposed to pharmacological amounts of nicotine, the tracer amount of nicotine we used (20 ng) does not influence CBF. 3 H-nicotine CBF measurements have been validated with 14 C-iodoantipyrine CBF measurements. We do not think that measurement of CBF with 3 H-nicotine affected the results of our study.

Conclusions
In summary, the principle finding of our study is that activation of K<sub>ATP</sub> channels do not contribute to cerebral vasodilatation after hemodilution. Consistent with prior investigators, we found that K<sub>ATP</sub> channels do contribute to cerebral vasodilatation during hypoxia. This supports the hypothesis that intravascular P<sub>O</sub><sub>2</sub> is an important independent regulator of CBF, and intravascular P<sub>O</sub><sub>2</sub> act in part via activation of K<sub>ATP</sub> channels.

References
Owing largely to its common use during cardiopulmonary bypass, the effects of hemodilution on cardiovascular homeostasis have been studied for more than 30 years. Already in 1967 it was recognized that hemodilution increased cerebral perfusion, and not long thereafter it was considered for treatment of acute head injury. In the following years, many studies examined the cerebrovascular effects of hemodilution in relation to blood flow distribution, cerebral metabolic rate, systemic hemorrhage, cerebral ischemia, cerebral autoregulation, hypopcapnia, vasospasm, and stroke. Despite these many studies, the mechanisms whereby hemodilution produces cerebral vasodilation remain uncertain.

Early hypotheses that arterial oxygen delivery was the primary variable influencing cerebral perfusion predicted that the mechanisms governing cerebrovascular responses to acute hypoxia and hemodilution might be similar because both perturbations decreased arterial oxygen content. It soon became quite evident, however, that blood viscosity influenced cerebral perfusion independent of changes in oxygen transport even though other evidence strongly suggested that tissue hypoxia was involved in responses to hemodilution. Further studies demonstrated that cerebrovascular responses to hemodilution were highly heterogeneous with a dependence on artery size, had little effect on microvascular pressure, and were mediated by a different combination of mechanisms than those governing responses to acute hypoxemia alone.

In light of these observations, contemporary views of the cerebrovascular effects of hemodilution credit the response to simultaneous effects on both arterial oxygen content and blood viscosity.

Based on the reasonable premise that reduced blood viscosity should attenuate endothelial shear stress and may thereby alter endothelial NO production, Todd and coworkers recently explored the role of NO in hemodilution-induced cerebral vasodilatation but found it played no role. The same conclusion has also been reached in recent separate studies by Plochl et al. Following the ideas that hemodilution-induced vasodilatation involves tissue hypoxemia and that both coronary and cerebrovascular responses to hypoxemia are mediated in large part via activation of ATP-sensitive potassium channels, the most recent efforts by Todd and coworkers (see the accompanying article) evaluate the effects of the K<sub>ATP</sub> channel antagonist glibenclamide on cerebrovascular responses to hemodilution. Further strengthening the established view that responses to hypoxia and hemodilution are mediated by different mechanisms, glibenclamide attenuated cerebral responses to hypoxia but not to hemodilution. Thus, the mystery remains: how exactly does hemodilution produce cerebral vasodilatation? Even though we can now rule out involvement of K<sub>ATP</sub> channels, as well as NO, cGMP, and changes in microvascular pressure or myogenic activity, there are still many candidate mechanisms to explore. These include all shear-stress-sensitive signal transduction pathways and their potential coupling to vascular contractile activity and/or the release of vasoactive factors other than NO from endothelial or other blood-borne cells. Certainly, exploration of these many possibilities will require more time and patience, but the demonstrated persistence of investigators such as Todd and coworkers promises that this mystery will not be abandoned anytime soon.

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References


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