Inhibition of vascular ATP-sensitive K⁺ channels does not affect reactive hyperemia in human forearm

H. M. OMAR FAROUQUE AND IAN T. MEREDITH
Cardiovascular Research Centre, Monash Medical Centre and Monash University, Melbourne, Victoria, 3168, Australia
Submitted 8 April 2002; accepted in final form 23 October 2002

Farouque, H. M. Omar and Ian T. Meredith. Inhibition of vascular ATP-sensitive K⁺ channels does not affect reactive hyperemia in human forearm. Am J Physiol Heart Circ Physiol 284: H711–H718, 2003; 10.1152/ajpheart.00315.2002.—The extent to which ATP-sensitive K⁺ channels contribute to reactive hyperemia in humans is unresolved. We examined the role of ATP-sensitive K⁺ channels in regulating reactive hyperemia induced by 5 min of forearm ischemia. Thirty-one healthy subjects had forearm blood flow measured with venous occlusion plethysmography. Reactive hyperemia could be reproducibly induced (n = 9). The contribution of vascular ATP-sensitive K⁺ channels to reactive hyperemia was determined by measuring forearm blood flow before and during brachial artery infusion of glibenclamide, an ATP-sensitive K⁺ channel inhibitor (n = 12). To document ATP-sensitive K⁺ channel inhibition with glibenclamide, coinfusion with diazoxide, an ATP-sensitive K⁺ channel opener, was undertaken (n = 10). Glibenclamide did not significantly alter resting forearm blood flow or the initial and sustained phases of reactive hyperemia. However, glibenclamide attenuated the hyperemic response induced by diazoxide. These data suggest that ATP-sensitive K⁺ channels do not play an important role in controlling forearm reactive hyperemia and that other mechanisms are active in this adaptive response. Regional blood flow; ion channels; ischemia

REACTIVE HYPEREMIA REFERS to the phenomenon of increased blood flow that follows relief of ischemia and is a result of conduit and resistance vessel dilatation. Typically, maximal hyperemia is observed immediately after restoration of blood flow (initial phase), which then declines exponentially toward baseline flow over several minutes (sustained phase). Clarification of the mechanisms involved in reactive hyperemia is of importance in understanding the pathophysiology and treatment of myocardial and limb ischemia (34). Several factors have been implicated in the genesis of reactive hyperemia, including mechanical (7, 11) and neurogenic mechanisms (32), endothelium-derived vasoreactive factors (13, 18, 39), adenosine (11), and membrane-bound ion channels (14, 41). Among the ion channels, there has been interest in the ATP-sensitive K⁺ channel and its role in blood flow regulation. These channels are activated by an increase in intracellular ADP and potassium channel-opening drugs, such as the antihypertensive agent diazoxide resulting in membrane hyperpolarization and vasodilation (40). In view of the biophysical characteristics of ATP-sensitive K⁺ channels, these channels may be active under conditions of ischemia and hypoxia. Indeed, studies in animals have demonstrated a role for ATP-sensitive K⁺ channels in coronary and skeletal muscle reactive hyperemia (2, 14, 17, 52).

Recent experiments have provided evidence for the existence of these channels in human smooth muscle cells (23, 33). We have demonstrated that ATP-sensitive K⁺ channels in the human coronary circulation may contribute to the regulation of resting coronary blood flow, adenosine-induced hyperemia, and metabolic coronary vasodilation (21, 22). In contrast, these channels may not contribute to exercise-induced forearm hyperemia (20). A few clinical studies have examined the role played by vascular ATP-sensitive K⁺ channels in skeletal muscle reactive hyperemia; however, these investigations have yielded conflicting results. These studies suggest that ATP-sensitive K⁺ channels may be involved in the initial phase (8, 31), or sustained phase of hyperemia (3, 4) but not both. Moreover, the magnitude of the contribution of ATP-sensitive K⁺ channels has varied among these studies. Thus the extent to which ATP-sensitive K⁺ channels contribute to peripheral blood flow regulation in human vasculature is unresolved. Therefore, the principal aim of this study was to determine the contribution of vascular ATP-sensitive K⁺ channels in reactive hyperemia by examining the effect of acute ATP-sensitive K⁺ channel inhibition with glibenclamide on postischemic forearm vasodilation in healthy humans.

MATERIALS AND METHODS

Subjects

The study population was 31 healthy subjects (age 23 ± 6 yr; 20 males and 11 females). All subjects were screened at an initial visit to determine suitability for the study. Exclusion criteria included the presence of conventional cardiovascular conditions.
Venous Occlusion Plethysmography

All studies were performed at the same time each morning in a quiet, temperature-controlled (22–23°C) vascular research laboratory as previously described (16, 39). In brief, subjects were fasted overnight and had abstained from caffeine- and alcohol-containing products for at least 12 h before the study. Brachial arterial cannulation was performed in the nondominant arm under aseptic conditions after adequate local anesthesia was achieved. Physiological saline was infused into the brachial artery at 0.4 ml/min to keep the catheter patent. Subjects were routinely rested in the supine position for a minimum of 30 min before the first forearm blood flow measurements were taken. Bilateral forearm blood flow was measured using the technique of venous occlusion plethysmography with a calibrated mercury-in-Silastic strain gauge (D. E. Hokanson, Bellevue, WA). A collecting cuff was wound around the upper arm and connected to a Hokanson E-20 rapid cuff inflator. The upper limb was supported above the level of the heart to ensure free venous drainage. The collecting cuff was rapidly inflated with air to a pressure of 40 mmHg in a cyclical fashion to occlude venous outflow. Hand blood flow was prevented by inflating a wrist cuff to a pressure of 200 mmHg during forearm blood flow recordings.

Blood Flow Measurements

Resting forearm blood flow was measured for a minimum of 2 min and an average of at least five stable measurements was used for analysis. Forearm reactive hyperemia was measured after deflation of an upper arm cuff that had been inflated to a pressure of 190 mmHg for 5 min. Flow measurements were recorded every 7 s for the first 2 min and then every 12 s for the next 3 min. Plethysmographic data and intra-arterial blood pressure were digitized on-line using an eight-channel analog-to-digital converter (MacLab/8s System, ADInstruments, Castle Hill, NSW, Australia) and analyzed off-line (Chart version 4.0.1, ADInstruments). Forearm blood flow was measured for 5 min after the ischemic stimulus and a flow versus-time curve constructed (Fig. 1).

Reproducibility of Reactive Hyperemia

To determine the reproducibility of the forearm ischemia protocol, blood flow was assessed during three periods of reactive hyperemia each separated by 15 min in nine healthy subjects. Five minutes of brachial artery occlusion induced reproducible reactive hyperemic blood flow responses (Table 2).

Drugs

Glibenclamide lyophilisate (kindly supplied by Aventis Pharma Deutschland, Frankfurt, Germany) was used as an inhibitor of vascular ATP-sensitive K+ channels in this study. Its specificity for ATP-sensitive K+ channels in vascular tissue has been demonstrated in humans (9) and animals (17). Glibenclamide lyophilisate is a stable preparation suitable for parenteral human use and does not require the addition of an alkaline vehicle to ensure solubility. Glibenclamide was dissolved in 0.9% saline (vehicle) and infused at 15 µg/min into the brachial artery by computerized syringe pump (Terumo, Tokyo, Japan) at 0.4 ml/min. Assuming resting forearm blood flow is 3 ml·100 ml−1·min−1, this infusion regimen would result in a regional plasma concentration of ~500 ng/ml. This level is at the upper end of the concentration range observed in venous blood at a mean of 3 h after the administration of a single 20-mg oral dose of glibenclamide to patients with Type 2 diabetes mellitus (12). Diazoxide (David

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**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>22 ± 4</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>7/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22 ± 2</td>
<td>23 ± 3</td>
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<tr>
<td>Total cholesterol, mmol/l</td>
<td>3.9 ± 0.6</td>
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<tr>
<td>LDL cholesterol, mmol/l</td>
<td>2.4 ± 0.5</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>0.9 ± 0.5</td>
<td>0.9 ± 0.5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61 ± 9</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>80 ± 3</td>
<td>91 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 22 subjects. M, male; F, female.
Table 2. Reproducibility of reactive hyperemia

<table>
<thead>
<tr>
<th></th>
<th>RHBF 1</th>
<th>RHBF 2</th>
<th>RHBF 3</th>
<th>P</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak RHBF, ml·100 ml⁻¹·min⁻¹</td>
<td>30.4 ± 3.0</td>
<td>29.3 ± 3.2</td>
<td>30.0 ± 2.7</td>
<td>0.52*</td>
<td>0.97</td>
</tr>
<tr>
<td>Minimum FVR, units</td>
<td>3.2 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>0.36*</td>
<td>0.98</td>
</tr>
<tr>
<td>Volume repaid at 1 min, ml/100 ml</td>
<td>13.5 ± 1.4</td>
<td>13.3 ± 1.2</td>
<td>12.8 ± 1.2</td>
<td>0.69*</td>
<td>0.83</td>
</tr>
<tr>
<td>Volume repaid at 5 min, ml/100 ml</td>
<td>27.0 ± 1.8</td>
<td>27.6 ± 2.0</td>
<td>26.3 ± 1.7</td>
<td>0.56*</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9 subjects. RHBF, reactive hyperemic blood flow; ICC, intraclass correlation coefficient. *Repeate-measures ANOVA.

Bull Laboratories, Melbourne, Australia), a vasodilator that acts by opening vascular ATP-sensitive K⁺ channels (43), was diluted in 5% dextrose and infused in graded doses of 1.9, 3.8, 7.5, and 15 mg/min into the brachial artery in protocol 2 (see below).

**Experimental Design**

Blood flow studies are schematically represented in Fig. 2.

**Protocol 1.** The contribution of vascular ATP-sensitive K⁺ channels to posts ischemic vasodilation was determined by measuring reactive hyperemia before and during infusion of glibenclamide lyophilisate, an inhibitor of the ATP-sensitive K⁺ channel (44, 50). Glibenclamide was infused at 15 μg/min into the brachial artery of 12 subjects by syringe pump for 30 min before blood flow measurements and continued during the period of ischemia and reactive hyperemia. Blood samples were taken before and after glibenclamide infusion for measurement of glucose, insulin, and C-peptide concentrations. C-peptide, an enzymatic cleavage product of proinsulin secreted from pancreatic β-cells with insulin in equimolar concentrations, was used as a confirmatory index of pancreatic insulin release.

**Protocol 2.** To assess the efficacy of ATP-sensitive K⁺ channel inhibition by glibenclamide lyophilisate, blood flow responses to graded infusions of diazoxide, an ATP-sensitive K⁺ channel opener, were determined in 10 subjects before and during coinfusion with glibenclamide.

**Calculations and Statistical Analysis**

All values are expressed as means ± SE and demographic data, as means ± SD. Forearm vascular resistance (expressed as units indicating mmHg·ml⁻¹·100 ml tissue⁻¹·min⁻¹ forearm tissue) was calculated from the quotient of mean arterial blood pressure and forearm blood flow. The blood volume repaid (or total hyperemic volume) after 1 and 5 min after release of arterial occlusion (Fig. 1) was determined by estimating the area under the flow-versus-time curve (35). To account for changes in resting blood flow, the absolute increase in peak reactive hyperemic blood flow and absolute volume repaid at 1 and 5 min was calculated by subtracting baseline resting forearm blood flow from the blood volume repaid at these time intervals. The sample size in protocol 1 was on the basis of a calculation showing that 12 subjects would be required to demonstrate a 30% difference in the 5-min hyperemic volume at a P value of 0.05 with 90% power. Reproducibility of reactive hyperemia was assessed using repeated-measures ANOVA and the intraclass correlation coefficient. The paired Student’s t-test was used to compare biochemical data and hemodynamic variables at rest and after ischemia before and after glibenclamide lyophilisate infusion. Two-way repeated-measures ANOVA was used to compare the effect of glibenclamide lyophilisate on the dose-flow response relationship to graded infusions of diazoxide. Statistical significance was accepted when P was < 0.05.

**RESULTS**

**Effect of Glibenclamide on Resting Forearm Blood Flow**

Glibenclamide infused for 30 min at 15 μg/min did not alter resting forearm blood flow or forearm vascular resistance (Table 3). Compared with vehicle, glib-
enclamide did not change mean arterial pressure (78 ± 1 vs. 79 ± 1 mmHg; P = 0.40) after 30 min of infusion.

**Effect of Glibenclamide on Forearm Reactive Hyperemia**

Glibenclamide did not affect the peak or sustained phase of reactive hyperemia (Table 3). There was a trend to increase in minimum forearm vascular resistance with glibenclamide (3.0 ± 0.2 vs. 3.9 ± 0.6 units; P = 0.10) due to a small rise in mean arterial pressure. Glibenclamide induced a decrease in serum glucose from 4.7 ± 0.1 to 3.8 ± 0.1 mmol/l (P < 0.001) and an increase in plasma insulin from 8.3 ± 0.9 to 11.2 ± 0.7 mU/l (P < 0.01). There was a concomitant rise in plasma C-peptide concentration from 0.7 ± 0.1 to 0.8 ± 0.1 nmol/l (P = 0.001). Contralateral forearm blood flow was unchanged.

**Effect of Glibenclamide on Diazoxide-Induced Vasodilation**

Diazoxide elicited a dose-related increase in blood flow in the infused forearm (P = 0.004; Fig. 3). Forearm blood flow increased nearly fivefold, from 3.5 ± 0.4 ml·100 ml⁻¹·min⁻¹ during vehicle infusion to 15.3 ± 2.9 ml·100 ml⁻¹·min⁻¹ at the highest diazoxide dose. Coinfusion of glibenclamide attenuated the vasodilator response induced by diazoxide (P = 0.02, ANOVA; Fig. 3). A downward shift of the dose-response curve was noted with the reduction in diazoxide-induced hyperemia being apparent at the upper end of the dose-response relationship. Coinfusion of glibenclamide resulted in a 20% decrease in stimulated blood flow at the highest diazoxide dose (15 mg/min; P = 0.002) and a 23% decrease at the preceding diazoxide dose (7.5 mg/min; P = 0.02). There was no significant alteration to mean arterial pressure or contralateral forearm blood flow during the dose-response study.

**DISCUSSION**

In this study, we demonstrate that glibenclamide, a specific inhibitor of the ATP-sensitive K⁺ channel, does not significantly alter resting blood flow or the hyperemic response to 5 min of ischemia in the forearm circulation of healthy humans. Our findings suggest that vascular ATP-sensitive K⁺ channels do not significantly contribute to the regulation of forearm blood flow at rest or during reactive hyperemia in healthy subjects.

**Resting Forearm Blood Flow**

Many animal studies using different experimental approaches have demonstrated that basal coronary arterial tone is, in part, dependent on the activity of ATP-sensitive K⁺ channels (17, 27, 49). However, the contribution of ATP-sensitive K⁺ channels to regulation of resting tone in animal skeletal muscle vasculature is less certain with some studies (29, 52) but not all (48), implicating ATP-sensitive K⁺ channels. In other vascular beds, such as the cerebral and renal circulations, ATP-sensitive K⁺ channels do not appear to contribute to the maintenance of basal tone but may be an important mechanism of vasodilation in certain pathophysiological states (5, 19, 46).

The contribution of ATP-sensitive K⁺ channels to blood flow regulation in humans has been examined using the technique of venous occlusion plethysmography. In one of the early studies, a single oral dose of glibenclamide was found to induce a significant reduction of resting calf blood flow in healthy subjects at 1 and 2 h after drug ingestion (31). This finding is in contrast to the data presented in our study and from other investigators in which no alteration to resting blood flow with ATP-sensitive K⁺ channel inhibition was noted (3, 4, 8). It may be of relevance that these studies have examined forearm blood flow rather than calf blood flow. Although lower and upper limb blood flow measurements with plethysmography primarily reflect skeletal muscle perfusion, there may be differences in blood flow regulatory mechanisms between these vascular beds (47). Moreover, in these negative studies, sulfonylurea ATP-sensitive K⁺ channel inhib-
itors have been infused directly into the forearm circulation of the experimental arm, thereby minimizing any potential systemic effects that may occur with oral administration. The finding that ATP-sensitive K\(^+\) channels do not appear to contribute to basal vascular tone in the human forearm may reflect inactivity of these channels under resting conditions due to the presence of physiological concentrations of intracellular ATP. However, the absence of a role for ATP-sensitive K\(^+\) channels in mediating basal forearm vascular tone should not necessarily be extrapolated to other vascular beds in humans, or to other situations, such as chronically ischemic muscle, in which blood flow may be more dependent on ATP-sensitive K\(^+\) channels.

**Reactive Hyperemia**

The contribution of vascular ATP-sensitive K\(^+\) channels to early and late phases of reactive hyperemia in animals is well established. Hyperemia after brief or prolonged coronary occlusions (≤45 min) can be attributed to ATP-sensitive K\(^+\) channel activation (2, 14, 15, 17). These channels have also been implicated in skeletal muscle reactive hyperemia (52). In light of the experimental data, a small number of studies have examined the role played by ATP-sensitive K\(^+\) channels in human reactive hyperemia. Kosmas et al. (31) examined calf reactive hyperemia after 10 min of femoral arterial occlusion before and after oral glibenclamide in healthy subjects. Glibenclamide was associated with a significant reduction in peak reactive hyperemia of 28% at 2 h after drug ingestion, but there was no change in reactive hyperemic volume after accounting for differences in baseline flow. These findings are in contrast to another study, which examined the contribution of ATP-sensitive K\(^+\) channels to forearm reactive hyperemia, induced by 5 min of ischemia (3). Blood flow responses were assessed before and during brachial artery infusion of the sulfonylurea tolbutamide in healthy subjects. This group reported no change in peak blood flow but a significant 27% reduction in reactive hyperemic volume at 5 min after cuff deflation.

Bijlstra et al. (8) studied forearm reactive hyperemia before and during brachial artery infusion of glibenclamide (infusion rate of \(~3 \mu g/min\)) in 12 healthy subjects. After 2 min of forearm ischemia, there was a significant 9% reduction in peak hyperemia and a 19% reduction in total flow debt repayment at 1 min after cuff deflation. Surprisingly, longer periods of forearm ischemia (5 and 13 min) did not result in significant changes to peak hyperemia or total flow debt repayment, although a small increase in minimum forearm vascular resistance was noted after the longer occlusion period. More recently, Bank et al. (4) reported that brachial arterial glibenclamide infusion at 100 \(\mu g/min\) did not reduce peak hyperemic blood flow after 5 min of forearm ischemia but did attenuate reactive hyperemic volume by 19% at 2 min after cuff deflation in nine healthy subjects. The findings of these studies, while conflicting as to the magnitude and timing of contribution by ATP-sensitive K\(^+\) channels, have, in general, supported a small-to-modest role for these channels in reactive hyperemia. Our data do not support these observations.

**Evidence for Vascular ATP-Sensitive K\(^+\) Channel Inhibition**

Glibenclamide is a potent and specific inhibitor of ATP-sensitive K\(^+\) channels (17, 44, 50) and is widely used to examine the contribution of ATP-sensitive K\(^+\) channels in blood flow regulation. The ability of glibenclamide to reduce the dilator response to potassium channel opening drugs, such as pinacidil and diazoxide, is often used in experimental settings to confirm ATP-sensitive K\(^+\) channel inhibition (17, 29, 48). Given that glibenclamide infused intra-arterially at 15 \(\mu g/min\) did not alter forearm blood flow at rest or after ischemia in this study, it was important to demonstrate that vascular ATP-sensitive K\(^+\) channel inhibition was achieved. We observed a modest reduction in diazoxide-induced vasodilation at the upper end of the dose-response curve in keeping with ATP-sensitive K\(^+\) channel inhibition. These findings concur with a previous study (9) in humans using brachial arterial infusions of glibenclamide. Although the vasodilator action of diazoxide has been attributed in large part to an opening of vascular ATP-sensitive K\(^+\) channels (37, 43, 44), the persistence of vasodilator activity in the presence of glibenclamide in this and other studies suggests that ATP-sensitive K\(^+\) channel-independent effects may also be operative, as has been demonstrated for other drugs in the class (38).

**Methodological Considerations**

We observed a small but significant rise in plasma insulin and C-peptide levels and a reduction in plasma glucose consistent with the effect of glibenclamide on the pancreas. Insulin is known to augment skeletal muscle blood flow and its vasodilator properties are primarily mediated by endothelial nitric oxide release (6), although other mechanisms including the activation of ATP-sensitive K\(^+\) channels may be involved (36). It is possible that the increase in insulin opposed the vasoconstrictor effects of vascular ATP-sensitive K\(^+\) channel inhibition. However, the vasoactive effects of insulin are delayed in onset and tend to occur at higher concentrations than the low physiological levels observed during this study (6). Moreover, in previous experiments, we have found no correlation between plasma insulin levels in the low physiological range and forearm blood flow (H. M. O. Farouque, unpublished observations). Insulin-induced hypoglycemia is also known to increase forearm blood flow and this effect appears to be mediated by \(\beta\) adrenoreceptors (24). However, it is unlikely that a greater hyperemia would have resulted at the glucose levels observed in the present study. Accordingly, the small changes observed in these humoral parameters are unlikely to have contributed to the lack of effect by glibenclamide on reactive hyperemia.
Failure to observe a reduction in reactive hyperemia with vascular ATP-sensitive K⁺ channel inhibition could also be due to the upregulation of other pathways involved in the control of vascular tone. It is conceivable that nitric oxide or prostacyclin-mediated vasodilation may compensate for the effect of ATP-sensitive K⁺ channel inhibition. The compensatory effect of alternative vasodilator systems has been elegantly demonstrated in a study by Ishibashi et al. (28) in which multiple vasodilator mechanisms were simultaneously inhibited in the coronary circulation of dogs.

Five-minute forearm ischemic periods may not be sufficient to cause alterations to intracellular nucleotide concentrations and activate ATP-sensitive K⁺ channels. It is conceivable that ATP-sensitive K⁺ channels are more likely to be activated after longer periods of forearm ischemia, which may result in a greater disturbance in muscle energy metabolism. Indeed, a recent study found that phosphocreatine and ATP concentrations, as determined by magnetic resonance spectroscopy, did not vary in gastrocnemius muscle during serial 5-min calf ischemia-reperfusion cycles (10). It is known that prolonged ischemic times result in a more pronounced sustained phase of reactive hyperemia although the peak response is similar (42). However, in the one study that has examined this issue, ATP-sensitive K⁺ channels did not play a greater role after longer periods of forearm ischemia (8). A difficulty in studying reactive hyperemia after longer periods of forearm ischemia is the discomfort that may be induced, resulting in recruitment of confounding autonomic reflexes. For these reasons, 5 min of forearm ischemia is frequently used. Indeed, many studies that have implicated mediators, such as nitric oxide and the vasodilator prostanooids in reactive hyperemia, have used this duration of ischemia (18, 30, 39).

Subjects in the present study were free of cardiovascular and other diseases. It may be that ATP-sensitive K⁺ channels play a prominent role in controlling vascular tone under conditions of disease (26) when other pathways of vasoregulation are impaired. It is also possible that muscle blood flow during chronic ischemia or recurrent episodes of acute ischemia is more dependent on ATP-sensitive K⁺ channels.

Physiological and Clinical Implications

Results of this study do not provide support for an important role of vascular ATP-sensitive K⁺ channels in the control of forearm reactive hyperemia in healthy young subjects. We (20) have recently shown that ATP-sensitive K⁺ channels also do not contribute to forearm metabolic vasodilation after isotonic forearm exercise. However, in the human coronary circulation of patients with atherosclerosis, these channels appear to be active and to participate in the regulation of coronary blood flow (21, 22). Thus there appear to be differences in the mechanisms of vasoregulation between peripheral and coronary circulations in vivo, which might be a reflection of the unique characteristics of each tissue and its associated vascular bed. The physiological relevance of these differences with respect to ATP-sensitive K⁺ channels is unclear. It might be that vascular ATP-sensitive K⁺ channels are more active in tissues that are vulnerable to ischemia, such as the myocardium, although this is speculative. The impact of variables, such as age, gender, and risk factors for atherosclerosis and other diseases on the activity of vascular ATP-sensitive K⁺ channels in the human circulation is unknown. It is possible that some of these factors may contribute to the differences in response to ATP-sensitive K⁺ channel inhibition between coronary and peripheral circulations.

Our data raise the possibility of a pharmacodynamic interaction between sulfonylureas and the ATP-sensitive K⁺ channel openers. ATP-sensitive K⁺ channel openers, such as nicorandil, are a relatively new class of drug introduced for the treatment of angina (51a). The efficacy of nicorandil is related to its coronary and peripheral vasodilator actions (25, 51). Given that diabetes mellitus is one of the major risk factors for ischemic heart disease, the potential for combined administration of sulfonylureas and nicorandil exists. A recent study has shed light on the molecular basis for an interaction between nicorandil and sulfonylureas (45). With the use of electrophysiological techniques in cells made to express recombinant ATP-sensitive K⁺ channels, nicorandil was found to activate smooth muscle and cardiac muscle variants of the ATP-sensitive K⁺ channel. Glibenclamide and gimepiride inhibited both smooth muscle and cardiac ATP-sensitive K⁺ channels. On the basis of these data, it is conceivable that clinically significant drug interactions may occur with coadministration of certain sulfonylureas and ATP-sensitive K⁺ channel openers.

We have demonstrated that acute vascular ATP-sensitive K⁺ channel inhibition does not significantly alter resting blood flow or the peak and sustained phases of reactive hyperemia in the forearm circulation of healthy young individuals.

We thank Kais Hamza, Department of Mathematics and Statistics, Monash University, for assistance with statistical analyses. We are grateful to Michael Zhang and Mauro Baldi for technical assistance.

H. M. O. Farouque is supported by a National Heart Foundation of Australia Medical Postgraduate Research Scholarship PM98M-0006.

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