Hypercapnia-induced cerebral and ocular vasodilation is not altered by glibenclamide in humans

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The study protocol was approved by the Ethics Committee of the Vienna University School of Medicine. The investigation conforms with the principles outlined in the Declaration of Helsinki. The nature of the study was explained, and all subjects gave written consent to participate. Fifteen male healthy volunteers were studied (age range, 20–35 yr; mean ± SD, 27 ± 4 yr). Each subject passed a screening examination that included medical history and physical examination, 12-lead electrocardiogram, complete blood count, activated

Subjects

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GLIBENCLAMIDE INFLUENCE ON HYPERCAPNIC VASODILATION

Partial thromboplastin time, thrombin time, fibrinogen, clinical chemistry (sodium, potassium, creatinine, uric acid, glucose, cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, total bilirubin, total protein), standardized oral glucose tolerance test, hepatitis A, B, C, and HIV serology, urine analysis, and a urine drug screen. Subjects were excluded if any abnormality was found as part of the screening unless the investigators considered an abnormality clinically irrelevant. Furthermore an ophthalmic examination, including slit-lamp biomicroscopy and indirect funduscopy, was performed in each subject before the first study day.

Inclusion criteria were normal ophthalmic findings and a refractive error of less than 3 diopters. Subjects did not take any nontrial medication, including over-the-counter drugs, throughout the study and were asked to abstain from alcohol and beverages containing xanthine derivatives for 12 h before drug administration. On each trial day subjects arrived after an overnight fast. Washout periods between study days were at least 5 days.

Study Protocols

Protocol 1. Ten healthy subjects were studied according to a randomized, double-masked, balanced, two-way crossover study design. After resting for at least 20 min in the sitting position to establish stable hemodynamic conditions, baseline measurements of fundus pulsation amplitude (FPA), sonography of the cerebral and the ophthalmic artery (OA), and a blood gas analysis were performed. Thereafter a 12-min inhalation period of 5% CO2-95% air was started and the measurements were repeated. After a resting period of 18 min, drug treatment was started and subjects received either glibenclamide (5 mg po; Glyburid Euglucon, 5 mg, Hoechst) and placebo intravenously or oral placebo and intravenous insulin (0.3 mU·kg⁻¹·min⁻¹; Lilly Huminsulin, Lilly; Fegersheim, France). To maintain euglycemic conditions, venous blood glucose was measured at regular intervals in arterialized venous blood from the heated contralateral arm and glucose (20% glucose, Leopold Infusionsflaschen, Leopold Pharma; Linz, Austria) was infused to achieve a blood glucose concentration of between 80 and 120 mg/dl. Every 30 min measurements of blood velocities with ultrasound sonography and FPA with laser interferometry were undertaken, and every 60 min a 12-min inhalation period of 5% CO2-95% air was repeated. Blood gas analysis was performed at baseline and during every inhalation period after 5 min of CO2 inhalation (Fig. 1).

Blood pressure was measured in 5-min intervals during drug administration and until 20 min after the end of drug administration. Pulse rate was monitored continuously until the end of drug administration. The subjects were monitored until at least 3 h after the end of the study. During this time period, their blood glucose concentration was measured at regular intervals.

Protocol 2, control experiments. To investigate whether glibenclamide exerts an effect on vascular KATP channels, a control experiment in five healthy subjects was performed. The study design was randomized, three-way crossover. After subjects rested for at least 20 min in the supine position to establish stable hemodynamic conditions, baseline measurements of forearm blood flow using a plethysmographic method were performed.

Volunteers then received either nicorandil (40 mg po, Dancor, Merck; Darmstadt, Germany) or vehicle in the presence of glibenclamide (5 mg po, Glyburid Euglucon) or nicorandil alone on the three different trial days: day A, glibenclamide and nicorandil; day B, glibenclamide and vehicle; and day C, nicorandil.

If glibenclamide was administered subjects also received glucose intravenously (20% glucose, Leopold Infusionsflaschen, Leopold Pharma) to maintain euglycemic conditions. Nicorandil or vehicle was administered 120 min after glibenclamide administration. On trial day C nicorandil alone was administered after an equivalent resting period.

Forearm blood flow was measured in 15-min intervals during the study; blood pressure and pulse rate were measured every 5 min. Blood samples for the determination of insulin plasma levels were drawn at baseline and 90 and 210 min after glibenclamide administration.

Measurements

Blood pressure and pulse rate. Systolic, diastolic, and mean blood pressures (MAP) were measured on the upper arm by an automated oscillometric device (HP-CMS patient monitor, Hewlett Packard; Palo Alto, CA). Pulse rate was automatically recorded from a finger pulse-oxymetric device (HP-CMS patient monitor).

Fundus pulsations. Pulse synchronous pulsations of the eye fundus were assessed by laser interferometry on the subject's right eye. The method is described in detail by Schmetterer and Lexer (23). Briefly, the eye is illuminated by the beam of a single mode laser diode with a wavelength (λ) of 783 nm. The light is reflected at both the surface of the cornea

![fig1](http://ajpregu.physiology.org/DownloadedFrom/10.1210/ajpregu.95.6.1668)
and the retina. The two reemitted waves produce interference fringes from which the distance changes between cornea and retina during a cardiac cycle can be calculated. Distance changes between cornea and retina lead to a corresponding change in optical distance $|\Delta L(t)|$. This change in interference order can be evaluated by counting the fringes moving inward and outward during the cardiac cycle. Changes in optical distance $|\Delta L(t)|$, corresponding to the cornea-retina distance changes, can then be calculated by $\Delta L(t) = |\Delta L(t)|/2$. The maximum distance change is called the FPA and estimates the local pulsatile blood flow (21). FPA was calculated as the mean of at least five cardiac cycles. The short-term and day-to-day variability of the method is small, which allows detection of even small changes in local pulsatile blood flow following pharmacological stimulation (25). To obtain information on the choroidal blood flow, the macula, where the retina lacks vasculature, was chosen for measurements (27).

Color Doppler ultrasound. Mean flow velocity (MFV), peak-systolic flow velocity (PSV), and end-diastolic flow velocity (EDV) were determined in the right OA with color Doppler ultrasound (8) and in the middle cerebral artery (MCA) with transcranial ultrasound. MFV was measured manually as the time mean of the spectral outline. Measurements were performed with a 7.5-MHz probe in the OA and with a 2-MHz probe in the MCA (CFM 750, Vingmed Sound; Horten, Norway). The OA was measured anteriorly, at the point where it crosses the optic nerve. The sample volume marker was placed 25 mm posterior to the globe. The resistive index was calculated for both arteries as resistive index equals PSV – EDV/PSV. All parameters were determined as mean values over at least three cardiac cycles.

Blood gas analysis. Blood gas values were determined from capillary blood samples of the earlobe after the earlobe was covered with ointment containing nicotine and nonylnvanil lamid (Finalgon, Tomae; Biberach, Germany) to induce capillary vasodilation, a lancet incision was made. The arterialized blood was drawn into a thin-glass capillary tube. Arterial pH, $PCO_2$, and $PO_2$ were determined with an automatic blood gas analysis system (AVL 995-Hb; Graz, Austria).

Glucose utilization. The amount of glucose necessary to maintain euglycemic conditions from minute 60 to minute 90, from minute 120 to minute 150, and from minute 180 to minute 210 was calculated as a measure of drug-induced glucose utilization.

Determination of glucose and insulin plasma levels. Glucose concentration was determined by using the glucose oxidase method (Beckman, Glucose Analyzer II Beckman Instruments; Fullerton, CA). Plasma insulin concentrations were determined by using a double antibody RIA (Diagnostic Systems Laboratories; Webster, TX).

Forearm blood flow. Forearm blood flow was measured by venous occlusion plethysmography, using a mercury-filled Silastic strain-gauge plethysmograph (EC-6, Hokanson; Washington, DC) (9). The forearm under study was placed above the level of the right atrium. Venous blood return from the arm was obstructed by inflating a cuff placed around the upper arm to 50 mmHg for 10 s. This inflated cuff caused swelling of the forearm at a rate proportional to the rate of arterial inflow. The rate of swelling of the forearm in milliliters per minute is calculated from changes of forearm circumference by a strain gauge placed around the forearm. The hands were excluded from the circulation by inflating a wrist-cuff to suprasystolic pressures. This method has been used repeatedly to assess effects of vasoactive drugs in human pharmacology studies (2).

**Data Analysis**

All statistical analyses were done using the Statistica software package (Release 4.5, StatSoft; Tulsa, OK). Reactivity of cerebral blood flow (CBF) to changes in $PCO_2$ has been calculated as $\Delta\ln CBF/\Delta\ln PCO_2 \times 100$ (30). MFV and FPA are not direct measures of total blood flow. Nevertheless we calculated the reactivity to changes in $PCO_2$ as $\Delta\ln MFV/\Delta\ln PCO_2 \times 100$ and $\Delta\ln FPA/\Delta\ln PCO_2 \times 100$ for each subject after glibenclamide administration and after insulin infusion for better comparison with other published data. Reactivity of hemodynamic parameters to changes in $PCO_2$ were analyzed with repeated measures ANOVA during the different treatments. Data are presented as means ± SE. The effect of hypercapnia was expressed as percent change of the corresponding values preceding the breathing periods. Post hoc analysis was done with paired t-tests. $P < 0.05$ was considered the level of significance. In protocol 2 changes in forearm blood flow were analyzed with repeated measures ANOVA during the different treatments. Plasma levels of insulin were compared by using the Wilcoxon ranked signs test.

**RESULTS**

**Protocol 1**

Baseline values of the measured parameters are presented in Table 1. There were no significant differences between the 2 study days at baseline.

**Effects of CO2 Inhalation**

$CO_2$ breathing significantly increased FPA and MFV in the MCA under baseline conditions (Fig. 2 and Table 2). The increase in FPA was 18.2 ± 2.8% ($P < 0.001$) and 22.3 ± 3.4% ($P < 0.001$) on the 2 trial days, respectively (Fig. 2). The increase in MFV in the MCA was 27.4 ± 4.1% ($P < 0.001$) and 33.3 ± 5.0% ($P < 0.001$). The reactivity to hypercapnia was higher in the MCA and in the choroid than in the OA (Table 2), where no significant increase in MFV was seen during baseline measurements ($2.1 \pm 3.5\%$, $P = 0.6$, and $6.5 \pm 4.5\%$, $P = 0.2$, Fig. 2). As expected, breathing of 5% $CO_2$-95% air significantly increased $PCO_2$ and $PO_2$ and caused a significant decrease in pH (Table 3).

**Effects of CO2 Inhalation During Low-Dose Insulin**

Insulin alone did not exert any effects on outcome parameters under study (Fig. 2). During the three $CO_2$ inhalation periods, FPA increased by 18.8 ± 3.4% ($P < 0.001$), MFV increased by 2.8% ($P = 0.6$), $P = 0.6$ and 6.5 ± 3.4% ($P < 0.001$). The level of significance. In protocol 2 changes in forearm blood flow were analyzed with repeated measures ANOVA during the different treatments. Plasma levels of insulin were compared by using the Wilcoxon ranked signs test.

**Table 1. Baseline ocular hemodynamic parameters of the 2 study days (protocol 1)**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Glibenclamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>Mean flow velocity in OA, cm/s</td>
<td>20.3 ± 1.4</td>
</tr>
<tr>
<td>Mean flow velocity in MCA, cm/s</td>
<td>56.7 ± 3.4</td>
</tr>
<tr>
<td>Fundus pulsation amplitude, μm</td>
<td>3.5 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n = 10$ subjects. OA, ophthalmalic artery; MCA, middle cerebral artery.
This increase was not different from baseline responsiveness to hypercapnia as indicated by a comparable reactivity index (Table 2). The effect in the MCA was stronger with an increase in MFV of 27.7 ± 6.1% (P < 0.001 vs. preceding value), 27.9 ± 6.7% (P < 0.001 vs. preceding value), and 29.9 ± 5.4% (P = 0.004 vs. preceding value) during the three breathing periods. Again, reactivity was not different from baseline conditions (Table 2). In contrast, MFV in the OA was enhanced significantly only at single time points during insulin administration, resulting in a maximal increase of 7.8 ± 2.9% (P = 0.02 vs. preceding value, Fig. 2). PCO2, PO2, and pH changed significantly vs. preinhalation period (Table 3). Glucose utilization during the three observation periods increased significantly over time (Fig. 3).

Effects of CO2 Inhalation During Glibenclamide Administration

Glibenclamide alone did not exert any effects on outcome parameters under study (Fig. 2). During the three inhalation periods, FPA increased by 26.6 ± 5.5, 25.0 ± 4.0, and 27.5 ± 3.9%, respectively (P < 0.001 vs. preceding value, Fig. 2). The reactivity to hypercapnia was comparable with baseline conditions (Table 2). The increase of MFV in the MCA during the three inhalation periods was 33.7 ± 5.6, 32.7 ± 5.6, and 33.6 ± 4.1% (P < 0.001 vs. preceding value, Fig. 2). Again, reactivity to hypercapnia was not different from baseline conditions (Table 2). No significant effect on baseline measurements was observed in the OA after glibenclamide administration (maximum change 8.9 ± 5.0%, P = 0.1, Fig. 2). Although there was a slightly more pronounced effect of hypercapnia in the MCA and in the choroid during glibenclamide administration, no significant differences in FPA and MFV between treatment groups were detectable. Again, the changes in PCO2, PO2, and pH were in the same range as during the baseline inhalation period and significantly different from individual preceding values (Table 3). Glucose utilization during the different 30-min observation periods increased significantly and was comparable to the increase induced by insulin (Fig. 3).

Systemic Hemodynamic Effects

Systemic hemodynamics did not change under insulin or glibenclamide (Table 3). Hypercapnia caused a small increase in MAP and pulse rate during some breathing periods. However, these changes were small and not consistently observed.

Table 2. Reactivity to hypercapnia during administration of glibenclamide or insulin

<table>
<thead>
<tr>
<th></th>
<th>Insulin or Glibenclamide</th>
<th>Baseline</th>
<th>Inhalation period 1</th>
<th>Inhalation period 2</th>
<th>Inhalation period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundus pulsation amplitude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>3.6 ± 1.1</td>
<td>2.6 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>2.9 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>3.2 ± 0.5</td>
<td>3.7 ± 0.8</td>
<td>3.3 ± 0.6</td>
<td>3.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.5437</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean flow velocity in MCA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>4.7 ± 0.9</td>
<td>3.9 ± 0.6</td>
<td>4.0 ± 1.5</td>
<td>4.1 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>4.6 ± 0.9</td>
<td>4.3 ± 0.8</td>
<td>4.3 ± 0.7</td>
<td>4.4 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.9705</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean flow velocity in OA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.4 ± 0.6</td>
<td>1.1 ± 0.2</td>
<td>0.6 ± 0.5</td>
<td>1.2 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>1.2 ± 0.8</td>
<td>1.4 ± 0.7</td>
<td>0.3 ± 0.9</td>
<td>0.6 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.2705</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 subjects. Reactivity to hypercapnia was calculated as Δln CBF/Δln PCO2 × 100 and as Δln MFV/Δln PCO2 × 100. No difference in reactivity of cerebral blood flow (CBF) and mean blood flow velocity (MFV) was noted between trial days. Insulin results are shown for 9 subjects because recording of results was not possible in 1 subject due to technical problems.
Baseline values of the outcome parameters did not differ between the 3 study days (data not shown).

Forearm blood flow was unchanged during glibenclamide, but significantly increased following nicorandil alone by a maximum of 78.2 ± 42.8% vs. baseline (P = 0.041, ANOVA). By contrast, preceding administration of glibenclamide abrogated the effect of nicorandil on forearm flow (Fig. 4). As expected from protocol 1, glibenclamide alone did not exert any effect on systemic hemodynamic parameters. Administration of nicorandil slightly decreased mean arterial pressure by 14.6 ± 2.7% and increased pulse rate by 13.5 ± 12.5% vs. baseline (P = 0.03 and P = 0.66, ANOVA). This was also seen after glibenclamide with nicorandil, which resulted in a decrease of mean arterial pressure by 13.4 ± 3.8% vs. baseline, and an increase of pulse rate by 13.8 ± 8.9% vs. baseline (P = 0.16 and P = 0.43, ANOVA).

Insulin plasma levels markedly increased from 7.1 to a maximum of 35.2 µU/ml and from 8.5 to 41.7 µU/ml at 210 min after glibenclamide and glibenclamide with nicorandil coadministration, respectively (P = 0.04, Wilcoxon matched-pairs test). Nicorandil alone had no effect on plasma insulin.

### DISCUSSION

The purpose of this study was to examine whether inhibition of K<sub>ATP</sub> channel activation with glibenclamide influences the effects of hypercapnia on cerebral and ocular hemodynamics. In the present experiments the cerebral and ocular vascular bed was studied because the choroid and the MCA showed a high reactivity to increased PCO<sub>2</sub> in previous experiments (20, 22, 29). As expected, CO<sub>2</sub> inhalation caused a significant increase in FPA and MFV in the MCA. The increase in MFV in the OA during hypercapnia was...
much smaller and reached the level of significance only during some inhalation periods. The main finding of our experiments is that glibenclamide had no effect on hypercapnia-induced hemodynamic responses in healthy subjects. K
subscripts_ATP
channels are not only found in blood vessels but also in pancreatic β-cells, where insulin secretion is stimulated by blockade of K
subscripts_ATP
channels (4). Thus our experimental setup had to be controlled for hyperinsulinemia, because we have previously shown that insulin itself can increase ocular blood flow (24). Our results demonstrate that 1) indeed, a marked increase in plasma insulin was measurable after glibenclamide and that 2) the dose of exogenous insulin administered did not alter blood flow in the vascular beds under study. Our study design was therefore not affected by different baseline conditions. Although the profile of hyperinsulinemia in response to glibenclamide is different from the continuous insulin administration regimen, the glibenclamide-increased glucose requirement was comparable with that of insulin, at least at selected time points. Furthermore, measurements of reactivity to hypercapnia over time demonstrate that the inhalation stimuli were also robust against minor changes in circulating insulin levels.

It has been demonstrated previously that therapeutic concentrations of glibenclamide affect vascular K
subscripts_ATP
channels in the human forearm (3) after intra-arterial infusion. Because estimation of glibenclamide concentration in the cerebral and ocular beds is not possible, we investigated whether inhibition of K
subscripts_ATP
channel activation has an impact on blood flow in a different vascular bed and can be influenced by a potassium channel opening drug. Whereas nicorandil alone significantly increased forearm blood flow over baseline, no changes in forearm blood flow were observed after preceding administration of glibenclamide. This is of interest because we would have expected that the nitric oxide (NO) donor properties of nicorandil could still be detectable under glibenclamide conditions in the forearm. However, it is well known that NO donor drugs differ in their arteriovenous selectivity (16), and our results therefore argue that the contribution of NO release to the effect of nicorandil on the forearm vasculature is small, at least following systemic administration.

It may, however, be speculated that the release of vasoactive NO from nicorandil was responsible for the systemic hypotensive response, which was noted in the presence and absence of glibenclamide to a similar degree. Nevertheless, our data are in agreement with results from other vascular beds, showing that the effects of nicorandil, but not of nitroglycerin, were blunted by blockade of K
subscripts_ATP
channels in isolated canine coronary arteries (11, 31). It is therefore likely that the abrogation of nicorandil’s effects by glibenclamide in the forearm is due to inhibition of potassium channel activation rather than to other mechanisms. This suggests that the dose of glibenclamide in our experiment was also appropriate to inhibit activation of vascular K
subscripts_ATP
channel in other vascular beds in humans, even if drug levels are not accessible in these tissues.

In the present study P
subscripts_CO2
increased from ~38 to 44.5 mmHg and elicited a significant effect on cerebral and ocular blood flow on both study days. One limitation of the study is that for ethical reasons only a moderate increase in P
subscripts_CO2
can be studied, and we have not obtained a dose-response relationship to hypercapnia. It was demonstrated in animal experiments that application of glibenclamide significantly reduced the vasodilation of feline pial arterioles in response to hypercapnia (15). This was also observed in rabbit cerebral arterioles (6). Of note are the differences in P
subscripts_CO2 achieved during hypercapnic inhalation. For example, the blunted response of blood vessels during glibenclamide was observed at a P
subscripts_CO2 of 54 mmHg, but not at a P
subscripts_CO2 of 66 mmHg in rabbits. This suggests that vasodilation to high levels of hypercapnia may not be mediated by K
subscripts_ATP
channels but rather involve other mechanisms. Nevertheless, the vasodilatory changes observed in the subjects under study are of a physiologically relevant magnitude, and an important effect of K
subscripts_ATP
channel blockade should have been detectable in the present cohort.

In addition, pH decreased significantly during all inhalation periods, resulting in extracellular acidosis. It is known that acidosis causes vascular relaxation, which has already been demonstrated in isolated canine basilar artery rings (12). This effect is also reversible with glibenclamide, suggesting a stimulatory function of the metabolic status on K
subscripts_ATP
channels. Again, the changes in pH in response to CO
subscripts2
inhalation were consistent throughout the trial days and not affected by the drugs under study. Although we cannot discriminate whether extracellular acidosis is primarily responsible for vasodilation in the present study, animal experiments have postulated that glibenclamide could influence vascular effects from extracellular acidosis as well as from hypercapnia.

Limited reproducibility or sensitivity of the methods employed are unlikely to contribute to the negative findings of the present study. Laser interferometric measurement of fundus pulsations is highly reproducible and subject to a very small short-term intrindividual variability (26). Even though the reproducibility of MFV in the OA and in the MCA is smaller, the sensitivity of the methods used should have been appropriate to detect even minor hemodynamic changes by glibenclamide during hypercapnic vasodilation.

How can our negative findings be reconciled with previous results from animal and human studies? Species differences could account for our unexpected results because the K
subscripts_ATP
channel inhibitor tolbutamide had no significant effect on cerebral blood flow during hypoxia and hypercapnia in rats (19) and glibenclamide attenuated cerebral blood flow during hypoxia but not during hypercapnia in rat experiments (18), whereas the glibenclamide effect was shown in cats (15) and rabbits (6). Interestingly, NO synthase inhibition blunted hypercapnic vasodilation in a variety of species (10, 15). We have recently shown that hypercapnic vasodilation is also NO dependent in humans using the
same methods as in the present study (22). On the basis of our results we cannot rule out a possible interaction between the L-arginine-NO system and KATP channels as postulated from cat experiments (15), but the formation of endothelial NO seems to represent the predominant mediator of hypercapnic vasodilation in humans in vivo rather than effects of KATP channels.

In conclusion, we have demonstrated a strong vasodilatory response to hypercapnia in cerebral and ocular vessels. However, these potent effects were not influenced by systemic doses of glibenclamide, indicating minor contribution of vascular KATP channels on hypercapnic vasodilation in healthy humans in vivo.

Perspectives

The mechanism of hypercapnic vasodilation in the particularly sensitive cerebral and ocular vasculature is not directly comparable with animal physiology, and several species differences exist. It appears that the main regulator of the acute vasodilatory response to hypercapnia is the L-arginine-NO system, probably interacting with other mediators, but the contribution of KATP channels is small, at least in the physiological range of oxygen tension and pH changes.

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