Thiazide-Induced Vasodilation in Humans Is Mediated by Potassium Channel Activation

Peter Pickkers, Alun D. Hughes, Frans G.M. Russel, Theo Thien, Paul Smits

Abstract—Hydrochlorothiazide and indapamide are thought to exert their hypotensive efficacy through a combined vasodilator and diuretic effect, but in vivo evidence for a direct vascular effect is lacking. The presence and mechanism of a direct vascular action of hydrochlorothiazide in vivo in humans were examined and compared with those of the thiazide-like drug indapamide. Forearm vasodilator responses to infusion of placebo and increasing doses of hydrochlorothiazide (8, 25, and 75 μg ⋅ min⁻¹ ⋅ dL⁻¹) into the brachial artery were recorded by venous occlusion plethysmography. Dose-response curves were repeated after local tetaethylammonium (TEA) administration to determine the role of potassium channel activation and, in patients with the Gitelman syndrome, to determine the role of the thiazide-sensitive Na-Cl cotransporter in the vasodilator effect of hydrochlorothiazide. Vascular effects of hydrochlorothiazide were compared with those of indapamide in both normotensive (mean arterial pressure, 85±7 mm Hg) and hypertensive (mean arterial pressure, 124±16 mm Hg) subjects. At the highest infusion rate, local plasma concentrations of hydrochlorothiazide averaged 11.0±1.6 μg/mL, and those of indapamide averaged 7.2±1.5 μg/mL. In contrast to indapamide, hydrochlorothiazide showed a direct vascular effect (maximal vasodilation, 55±14%; P=0.013), which was inhibited by TEA (maximal vasodilation after TEA, 13±10%; P=0.02). The response was not dependent on blood pressure and was similar in patients with Gitelman syndrome, indicating that absence of the Na-Cl cotransporter does not alter the vasodilatory effect of hydrochlorothiazide. The vasodilator effect of hydrochlorothiazide in the human forearm is small and only occurs at high concentrations. The mechanism of action is not mediated by inhibition of vascular Na-Cl cotransport but involves vascular potassium channel activation. In contrast, indapamide does not exert any direct vasoactivity in the forearm vascular bed. (Hypertension. 1998;32:1071-1076.)

Key Words: hydrochlorothiazide ▪ indapamide ▪ vasodilation ▪ human ▪ potassium channels ▪ hypertension, essential ▪ Gitelman syndrome

Since the discovery of thiazide diuretics in 1957, thiazides have been the most prescribed drugs in the world, with thiazide diuretics exerting their effect in the kidney. However, the major hypotensive effect of thiazides during long-term administration appears to be due to vasodilation rather than to saluresis or loss of free water per se.1-3 It is unclear whether the vascular effects are mainly due to a direct interaction with the vascular wall4,5 or secondary to diuretic-induced changes in sodium balance.6-8 In animal and human isolated resistance arteries, hydrochlorothiazide exerts a dose-dependent direct vasodilator effect at therapeutically relevant concentrations. Since it is unknown whether the Na-Cl cotransporter is also present in vascular smooth muscle cells, inhibition of this cotransporter, the primary site of action in the kidney, has not been associated with the direct vascular effects of hydrochlorothiazide. Studies investigating the mechanism of this action revealed that it depended on activation of vascular potassium channels.9,10 The type of potassium channel activated appears to be the large-conductance calcium-activated potassium (KCa) channel since the vascular action of thiazides is inhibited by KCa blockers like tetraethylammonium (TEA),11 charybdotoxin,9,10,12 and iberiotoxin9 but not by blockers of other vascular potassium channels.9,10

In a previous in vivo study, the direct vasoactivity of hydrochlorothiazide could not be confirmed in the human forearm.13 Among other reasons, dosage of hydrochlorothiazide and initial level of blood pressure may have influenced the results, since the antihypertensive action is related to the initial blood pressure.14

Since indapamide is a thiazide-like agent with antihypertensive properties at doses that provoke minimal diuretic effects,15 its mode of action is thought to be due to a combined...
Vascular Action of Thiazides In Vivo

Baseline Demographic Characteristics of All Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensives</th>
<th>Hypertensives</th>
<th>Gitelman Syndrome</th>
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<tr>
<td>HR, bpm</td>
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Values are mean±SD. BMI indicates body mass index; FAV, forearm value; SBP, systolic blood pressure (measured intra-arterially); DBP, diastolic blood pressure (measured intra-arterially); and HR, heart rate (measured by ECG).

Methods

Subjects

After the approval of the ethics committee of our hospital and the written informed consent of each subject were obtained, we studied 24 normotensive volunteers, 12 hypertensive patients, and 2 patients with Gitelman syndrome. The Gitelman syndrome is characterized by the absence of the thiazide-sensitive Na-Cl cotransporter throughout the body. These patients represent a unique group to study the role of K<sub>Ca</sub> channel activation and Na-Cl cotransporter in the direct vascular action of hydrochlorothiazide. Furthermore, we wanted to compare the effects of hydrochlorothiazide with the thiazide-like agent indapamide, for which a vascular action is claimed to be even more pronounced.

Procedures

After local anesthesia (lidocaine 2%) was induced, the left brachial artery was cannulated with a 20-gauge catheter (Angiocath, Deseret Medical, Becton Dickinson) for drug infusion (automatic syringe infusion pump, type STC-521, Terumo) and blood pressure monitoring (Hewlett Packard GmbH). All blood pressures mentioned were acquired from these intra-arterial measurements. Mean arterial pressure (MAP) was determined by the electronically integrated area under the brachial arterial pulse-wave curve and averaged per forearm blood flow (FBF) measurement. A second catheter was inserted in a deep ipsilateral antecubital vein to obtain venous blood samples during the last minute of each infusion. Plasma concentrations of hydrochlorothiazide and indapamide were measured by high-performance liquid chromatography according to a previously described method. At least 30 minutes after intra-arterial cannulation and 1 minute after occlusion of the hand circulation (inflation of a wrist cuff to 200 mm Hg), FBF was measured in both arms 3 times a minute by ECG-triggered venous occlusion plethysmography with the use of mercury-in-Silastic strain gauges (Hokanson EC4, DE Hokanson). The upper arm collecting cuffs were simultaneously inflated to 45 to 50 mm Hg with a rapid cuff inflator (Hokanson E-20). FBF and drug administration (automatic syringe infusion pump, type STC-521, Terumo) were normalized to forearm volume as measured with the water displacement method and expressed in milliliters per minute per deciliter. Baseline FBF was measured for 5 minutes, during which vehicle control was infused, after which the increasing dosages of hydrochlorothiazide, indapamide, or norepinephrine were administered in a single-blind manner for 5 minutes each. Each measurement period lasted maximally 10 minutes and was alternated by a 5-minute pause, during which the wrist cuff was deflated to allow recovery of the hand circulation. The mean FBF of the last 2 minutes recorded at each infusion rate was taken as the response and used for further analysis. In the normotensive group, infusion of the highest dose of indapamide was continued for 20 minutes instead of 5 minutes.

Protocols

Direct Vascular Effects of Hydrochlorothiazide

Four protocols with hydrochlorothiazide were conducted.

Protocol A1: Effect of Hydrochlorothiazide in Normotensive and Hypertensive Subjects

In 6 normotensive subjects and in 6 hypertensive patients, hydrochlorothiazide was infused intra-arterially at a rate of 8, 25, and 75 μg·min⁻¹·dl⁻¹. The patients with essential hypertension were newly diagnosed or discontinued their medication 4 weeks before entering the study.

Protocol A2: Effect of Hydrochlorothiazide on Norepinephrine-Induced Vasocostriction

Long-term treatment with thiazides inhibits the vasoconstrictor action of norepinephrine in both normotensive and hypertensive subjects. To examine the acute effects of hydrochlorothiazide at a varying degree of plasma concentration, we measured the vasoconstrictor response to intra-arterially administered norepinephrine (10, 30, and 100 ng·min⁻¹·dl⁻¹) before and after local administration of hydrochlorothiazide (1.0 μg·min⁻¹·dl⁻¹) in 6 normotensive volunteers. There was a 30-minute pause between the 2 norepinephrine dose-response curves, and hydrochlorothiazide infusion was initiated before the second norepinephrine dose-response curve. Previous experiments revealed that intra-arterial infusion of this hydrochlorothiazide dose did not change basal FBF and led to clinically relevant concentration in the infused forearm.

Protocol A3: Involvement of Potassium Channel Activation in Hydrochlorothiazide-Induced Vasodilation

In vitro studies indicate that hydrochlorothiazide-induced vasorelaxation is mediated by K<sub>Ca</sub> channel opening. Since charybdotoxin andiberiotoxin (the 2 most selective blockers of the K<sub>Ca</sub> channel) are too toxic for human application, we chose TEA to investigate the role of K<sub>Ca</sub> channel activation in the vascular effects of hydrochlorothiazide. TEA has been used as a ganglion blocker in a total dose of 500 mg IV in patients with peripheral vascular disease and normal subjects. TEA antagonizes different types of potassium channels with varying degrees of potency, but the compound has been shown to selectively block single K<sub>Ca</sub> channels in arterial smooth muscle at
concentrations <1 mmol·L⁻¹. In the normotensive group of protocol A2 (n=6), we administered TEA intra-arterially at an infusion rate of 0.1 mg·min⁻¹·dL⁻¹, calculated to lead to a local plasma concentration of ~0.5 mmol·L⁻¹. The hydrochlorothiazide dose-response curve was repeated after a pause of 30 minutes and 10 minutes of local TEA administration. TEA administration was continued during the hydrochlorothiazide infusions.

In a previous study we found that sodium nitroprusside–induced vasodilation was not inhibited by TEA, indicating that TEA is not a nonspecific inhibitor of vasodilation (P. Pickkers, unpublished data, 1998).

**Protocol A4: Involvement of Inhibition of Vascular Na-Cl Cotransport in Hydrochlorothiazide-Induced Vasodilation**
The renal effects of hydrochlorothiazide are the result of inhibition of the electrONEURAL Na-Cl cotransporter in the early segment of the distal tubule. The presence of this cotransporter in vascular smooth muscle cells and its possible role in modulation of vascular tone have not been determined. Two patients with the Gitelman syndrome who lack the NaCl cotransporter were studied during protocol A2, as described above.

**Direct Vascular Effects of Indapamide**

**Protocol B1: Effect of High-Dose Indapamide in Normotensive and Hypertensive Subjects**
Analogous to protocol A2 (see above), indapamide (8, 25, and 75 μg·min⁻¹·dL⁻¹) was infused intra-arterially in 6 normotensive and 6 hypertensive subjects. A previous set of experiments in normotensive volunteers using intra-arterial infusion rates of 0.1 to 10 μg·min⁻¹·dL⁻¹ revealed that this concentration range did not change FBF (n=6; data not shown).

**Drugs and Solutions**
On the day of use, hydrochlorothiazide, indapamide, and TEA were reconstituted from a sterile powder (Sigma), diluted in NaHCO₃ 1.4% (hydrochlorothiazide) or NaCl 0.9% (indapamide and TEA) to a concentration of 0.1, 0.1, and 1.0 mg·mL⁻¹, respectively, and passed through a 0.22-μm Millipore filter. Further dilutions were prepared immediately before the experiment. Norepinephrine (amplue 1 mg·mL⁻¹) was also freshly dissolved in NaCl 0.9% just before the experiment.

**Data Analysis, Calculations, and Statistics**
The effects of hydrochlorothiazide and indapamide were analyzed by comparing the hemodynamic variables at baseline and at the increasing dosages by 1-way ANOVA with repeated measures. Post hoc comparisons between the different dosages were made by Student’s t tests, including Bonferroni correction. Paired Student’s t tests were used for the assessment of the effect of TEA on baseline parameters. To evaluate the effect of potassium channel blockade on the hydrochlorothiazide responses, 2-way repeated-measures ANOVA was performed on the changes from baseline.

Comparisons of the effects between different groups was performed by 1-way ANOVA with repeated measures. The mean FBF of the last 2 minutes recorded at each infusion rate was taken as the response. Changes in FBF were compared with values obtained during baseline measurements and expressed as percent change in ratio of the infused and noninfused arms compared with the baseline ratio to correct for small baseline differences between the first and second parts of the experiment. By using the ratio of the FBF measurements, the noninfused arm can be considered a contemporaneous control for the infused arm.

All data are expressed as mean±SEM of n experiments, unless indicated otherwise. A P value <0.05 was considered statistically significant.

**Results**

**Effects of Hydrochlorothiazide in Normotensive and Hypertensive Subjects**
In normotensive subjects, basal FBF values in the experimental and control arms were 1.6±0.1 and 1.5±0.2 mL·min⁻¹·dL⁻¹, respectively. Infusions of 8, 25, and 75 μg·min⁻¹·dL⁻¹ hydrochlorothiazide led to local plasma concentrations of 0.8±0.18, 3.30±0.49, and 11.02±1.63 μg·mL⁻¹, respectively, and an increase in the ratio of the infused and noninfused forearms of 6±5%, 12±8%, and 55±14% (ANOVA with repeated measures, P=0.013), as shown in Figure 1 (left panel). Post hoc analysis revealed significant increases in FBF for the last 2 hydrochlorothiazide doses. No significant effects were detected on blood pressure (119±5/70±4 at baseline versus 122±4/69±3 mm Hg during infusion of the highest dose) (MAP, 86±4 versus 86±3), heart rate (57±1 versus 58±1 bpm), and FBF in the noninfused arm (1.5±0.2 versus 1.7±0.3 mL·min⁻¹·dL⁻¹). Similar results were obtained in hypertensive patients: basal FBF, blood pressure, and heart rate were 2.4±0.4 and 2.5±0.4 mL·min⁻¹·dL⁻¹, 163±8/102±9 mm Hg, and 62±4 bpm. Hydrochlorothiazide-induced vasodilation reached a maximum of 30±18%, but this failed to reach statistical signif-

**Figure 1.** Percent change in FBF ratio (infused/noninfused arm) during graded intrabrachial infusions of hydrochlorothiazide or indapamide compared with placebo infusion as measured by venous occlusion plethysmography (mean±SEM). The P value refers to the statistical analysis by ANOVA with repeated measures over the complete dose-response curve. Left, Direct vasoactivity of hydrochlorothiazide in normotensives (n=6; P=0.013), hypertensives (n=6; P=0.09), and patients with Gitelman syndrome (n=2). There were no significant differences between the groups studied. Right, Direct vasoactivity of indapamide in normotensives (n=6; P=NS) and hypertensives (n=6; P=NS).
Mechanism of Action of Hydrochlorothiazide-Induced Vasodilation

Role of K_{Ca} Channel Activation

Figure 2 demonstrates the inhibition of hydrochlorothiazide-induced vasodilation by TEA. TEA infusion into the brachial artery had no significant effect on baseline FBF (n=6; from 1.9±0.2 to 1.9±0.2 mL·min⁻¹·dL⁻¹ after 10 minutes; P=NS). Some subjects who were infused with TEA experienced paresthesia in the infused arm. In addition, fasciculations of the forearm muscles were occasionally observed. All symptoms disappeared within 10 minutes after termination of the TEA infusion. Throughout these experiments, there were no significant changes in contralateral FBF, blood pressure, and heart rate (data not shown).

Hydrochlorothiazide-induced vasodilation in the normotensive subjects was significantly attenuated when the dose-response curve was repeated in the presence of TEA (−7±4%, −9±9%, and 13±10% difference; P=0.02 compared with hydrochlorothiazide-induced vasodilation in the absence of TEA; see above).

Role of Na-Cl Cotransport Inhibition

In 2 patients with the Gitelman syndrome, basal blood pressure, heart rate, and FBF in the infused and noninfused arms were 104±7/58±6 mm Hg, 66±0.3 bpm, 1.6±0.4 mL·min⁻¹·dL⁻¹, and 2.5±0.1 mL·min⁻¹·dL⁻¹, respectively. Hydrochlorothiazide infusions increased FBF in the infused forearm (vasodilation in patient 1, 23%, 39%, and 100%; vasodilation in patient 2, 4%, −4%, and 26%), with no relevant effects on blood flow in the noninfused arm and the other hemodynamic parameters (Figure 1, left panel). The vasodilation in these 2 patients was not significantly different from that in normotensive and hypertensive subjects.

Effects of Indapamide in Normotensive and Hypertensive Subjects

During intra-arterial infusion of indapamide (infusion rate of 8, 25, and 75 μg·min⁻¹·dL⁻¹), plasma concentrations of indapamide were 0.45±0.06, 0.98±0.19, and 7.22±1.54 μg·mL⁻¹. Figure 1 (right panel) illustrates the vascular effects of intrabrachial infusion of these dosages of indapamide. No hemodynamic (blood pressure and heart rate) or direct vascular (FBF) effects were observed in normotensive subjects (blood pressure, 129±3/68±3 mm Hg) or in hypertensive patients (blood pressure, 161±13/91±5 mm Hg). Sustained infusion of the highest indapamide dose for 20 minutes did not change FBF.

Discussion

The main conclusions of the present study are that hydrochlorothiazide exerts a direct vasodilator effect in the human forearm at supratherapeutic plasma levels and that this action is mediated by activation of vascular potassium channels and not by inhibition of a putative vascular Na-Cl cotransporter. Furthermore, hydrochlorothiazide-induced vasodilation is not shared by the thiazide-like agent indapamide.

Although vascular effects of thiazide diuretics were suspected almost from their introduction in the late 1950s, no direct in vivo evidence was available. In experiments in which plasma volume and total peripheral vascular resistance were calculated before and after long-term treatment with hydrochlorothiazide, it was found that after weeks to months of treatment plasma volume returned to baseline values, whereas blood pressure was still suppressed. This indicated an attenuated peripheral resistance and thus vasodilation. Since then, there have been speculations regarding whether this action is due to a direct interaction with the vascular wall or secondary to the initial renal salt loss.

Previous studies have shown that long-term treatment with hydrochlorothiazide attenuated the vasoconstrictive effects of norepinephrine in both normal and hypertensive subjects. Various mechanisms of action could be responsible for this effect, e.g., a direct interaction with the α-receptor or through modulation of catecholamine plasma levels or the sympathetic nerve system. Our study indicates that there is no direct interaction between the α-receptor and hydrochlorothiazide. In addition, various in vitro studies with isolated animal and...
human resistance arteries have demonstrated convincingly that hydrochlorothiazide and related compounds exert a direct vasodilator effect.9-12,16 Subsequent experiments showed that this effect was mediated by opening of vascular calcium-activated potassium channels, resulting in hyperpolarization and reduction in intracellular calcium in the smooth muscle cell. The present study provides the first evidence that in vivo hydrochlorothiazide is also able to exert a direct vasodilator effect through activation of vascular potassium channels, independent of its renal effects.

Mechanism of Action of Hydrochlorothiazide-Induced Vasodilation

The principal renal site of hydrochlorothiazide action is the electroneutral Na-Cl cotransporter in the distal tubule.28 To our knowledge, it is unknown whether this cotransporter is also present in vascular smooth muscle cells and whether it is of importance in the vascular action of hydrochlorothiazide. Patients with the rare disease known as Gitelman syndrome are characterized by the absence of the thiazide-sensitive Na-Cl cotransporter.18 Since the vasodilator effect of hydrochlorothiazide was in the same order of magnitude in 2 of these patients compared with the controls, we conclude that presence of the Na-Cl cotransporter does not play an important role in this effect.

A wide range of vasodilatory compounds of different chemical structure have been found to act by opening of potassium channels.30,31 The direct vasodilator actions of thiazide diuretics on isolated vessels are associated with an increase in Rb\(^{+}\) efflux (as a marker for K\(^{+}\) efflux)\(^{10,32}\) and hyperpolarization of the plasma membrane and are inhibited by selective blockers of the K\(_{Ca}\) channel.9-12 From these experiments, the role of vascular potassium channel activation in the direct vascular activity of hydrochlorothiazide is evident. The present study provides evidence that the mechanism of action described in vitro is also operational in vivo.

The most important question—whether this direct vascular effect contributes to blood pressure–lowering efficacy—remains unanswered for several reasons. First, vasodilation in vivo is only achieved at plasma concentrations of hydrochlorothiazide that are higher than those normally reached during long-term oral treatment. However, both hydrochlorothiazide and indapamide are known to accumulate in vascular smooth muscle by inhibiting the slow inward calcium current.35 This accumulation of the diuretics in vascular smooth muscle may be needed to reach similar drug concentrations in the vascular smooth muscle cell compared with long-term systemic treatment with lower dosages. Somewhat counter to this view is the fact that the increase in FBF after hydrochlorothiazide administration reached steady state within 1 to 2 minutes, and prolongation of the highest dose of indapamide to 20 minutes had no additional effect. However, accumulation of the diuretics in vascular smooth muscle may take days to weeks rather than minutes. Second, blood pressure reduction after long-term treatment with diuretics is related to the level of initial blood pressure.14 By contrast, in our studies hydrochlorothiazide tended to induce less vasodilation in hypertensive patients, and we found no correlation between the initial blood pressure or forearm vascular resistance and the direct vascular effect of hydrochlorothiazide. It should be noted, however, that the hypertensive patients were significantly older that the normotensive controls and that factors such as age or endothelium damage may have influenced these results.

Whether the reduction in peripheral resistance after long-term therapy with hydrochlorothiazide is due to K\(_{Ca}\) channel activation is still unresolved. One option to investigate whether K\(_{Ca}\) channel activation is an important component in the reduction of peripheral resistance after long-term therapy with hydrochlorothiazide would be to assess the effect of potassium channel blockade on basal FBF. In our experiments, TEA had no significant effect on basal FBF, whereas under conditions when the K\(_{Ca}\) channel is activated, TEA may reduce FBF. This approach to demonstrate potassium channel activation has been reported before, since TEA had no effect on basal vascular tone of coronary arteries in the nonischemic myocardium but significantly reduced coronary blood flow in the ischemic heart, indicating that ischemia activates vascular potassium channels.33 Therefore, if long-term treatment with hydrochlorothiazide reduces peripheral vascular resistance by increasing the open-state probability of K\(_{Ca}\) channels in vascular smooth muscle cells, intra-arterial administration of an antagonist (eg, TEA) should decrease FBF.

Although the observed vasodilator action of hydrochlorothiazide is small, one should realize that the diuretic effects of hydrochlorothiazide prevent the normal counterregulatory effects of vasodilators, such as fluid and sodium retention. Therefore, a small vasodilator effect associated with the absence of counterregulatory sodium retention may well explain the efficacy of thiazides in the treatment of hypertension.

Indapamide

A wealth of data from animal experiments and clinical pharmacological studies, including long-term therapeutic trials, has established extensive knowledge of the vascular activity of indapamide. Nevertheless, direct indapamide-induced vasoactivity measured in humans in vivo has never been reported. Indapamide has been reported to increase resting muscle blood flow by 38% after 1 week of systemic treatment in patients with essential hypertension, as measured with a xenon washout technique,24 but whether this effect is due to a direct or indirect (eg, counterregulatory) effect is unclear. Data from in vitro experiments with animal tissue have shown that indapamide directly acts on vascular smooth muscle by inhibiting the slow inward calcium current.35 This results in a reduced \(^{45}\)Ca\(^{2+}\) uptake in arteries stimulated with norepinephrine or a depolarizing potassium solution16 and vasorelaxation at concentrations similar to those seen therapeutically in blood (IC\(_{50}\)=80 nmol·L\(^{-1}\) ).16 In these experiments, indapamide seems to exert calcium channel antagonistic effects. In contrast to the aforementioned results obtained from animal experiments, the lack of a direct vascular effect of indapamide in our experiments is in agreement with data from studies with isolated arteries of human origin.16 It appears that species differences explain these contradictory results and that human vessels may not be sensitive to indapamide. Our experiments exclude the pres-
ence of an acute, direct vascular effect of therapeutic and supratherapeutic plasma concentrations of indapamide in the human forearm of normotensive and hypertensive subjects.

In conclusion, we found that similar to in vitro experiments, hydrochlorothiazide exerts a direct vascular effect in vivo, probably mediated by activation of vascular potassium channels and unrelated to the presence of the Na-CI cotransporter. This direct interaction of hydrochlorothiazide with the vascular wall could contribute to its antihypertensive efficacy. Whether this mechanism is of importance during long-term systemic treatment remains to be established.

Acknowledgments

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References


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