Angiotensin II AT₁ Blockade Normalizes Cerebrovascular Autoregulation and Reduces Cerebral Ischemia in Spontaneously Hypertensive Rats

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Background and Purpose—Angiotensin II, through stimulation of AT₁ receptors, not only controls blood pressure but also modulates cerebrovascular flow. We sought to determine whether selective AT₁ antagonists could be therapeutically advantageous in brain ischemia during chronic hypertension.

Methods—We pretreated spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto controls with the AT₁ antagonist candesartan (CV-11974), 0.5 mg/kg per day, for 3 to 14 days, via subcutaneously implanted osmotic minipumps. We analyzed cerebral blood flow by laser-Doppler flowmetry, cerebral stroke in SHR after occlusion of the middle cerebral artery with reperfusion, and brain AT₁ receptors by quantitative autoradiography.

Results—Candesartan treatment normalized blood pressure and the shift toward higher blood pressures at both the upper and lower limits of cerebrovascular autoregulation in SHR. Candesartan pretreatment of SHR for 14 days partially prevented the decrease in blood flow in the marginal zone of ischemia and significantly reduced the volume of total and cortical infarcts after either 1 or 2 hours of middle cerebral artery occlusion with reperfusion, relative to untreated SHR, respectively. This treatment also significantly reduced brain edema after 2 hours of middle cerebral artery occlusion with reperfusion. In SHR, candesartan markedly decreased AT₁ binding in areas inside (nucleus of the solitary tract) and outside (area postrema) the blood-brain barrier and in the middle cerebral artery.

Conclusions—Pretreatment with an AT₁ antagonist protected hypertensive rats from brain ischemia by normalizing the cerebral blood flow response, probably through AT₁ receptor blockade in cerebral vessels and in brain areas controlling cerebrovascular flow during stroke.

Key Words: brain hypertension peptides receptors stroke

Angiotensin II (Ang II) contributes to modulate blood pressure by stimulation of Ang II AT₁ receptors in smooth muscle vascular cells, followed by vasoconstriction, and blockade of AT₁ receptors with selective nonpeptide inhibitors is an effective treatment of hypertension in humans.¹ Ang II receptors and angiotensin-converting enzyme (ACE) are present in cerebral microvessels and cerebral arteries,²–⁴ indicating that endogenous Ang II may modulate cerebrovascular flow. Blockade of Ang II formation by ACE inhibitors inhibits the vascular tone maintained by locally produced Ang II, resulting in vasodilatation of large cerebral arteries. The cerebral blood flow is theoretically maintained by compensatory vasoconstriction of smaller resistance arteries.⁵ Since these resistance arteries have a higher potential vasodilatory capacity during decreases in blood pressure and a lower vasoconstricting capacity during increases in blood pressure, the autoregulation is shifted toward lower pressures.⁶,⁷ Alterations in cerebrovascular autoregulation, with a shift toward higher blood pressures and a predisposition to ischemia and stroke, are present in genetic and experimental hypertension. Blockade of Ang II formation or bradykinin degradation with ACE inhibitors prevents and reverses these alterations, improves tolerance to hypotension,⁸ and protects against focal cerebral ischemia in spontaneously hypertensive rats (SHR).⁹,¹⁰ Acute administration of candesartan, a very potent AT₁ receptor antagonist, to SHR shifts their cerebrovascular autoregulatory response to the left, in the direction of lower blood pressures, in a manner similar to that of ACE inhibitors.¹¹ We sought to determine whether chronic administration of AT₁ antagonists could protect hypertensive rats from the effects of cerebral ischemia and whether this effect was related to modulatory effects in cerebral blood flow and/or to blockade of central AT₁ receptors.

Materials and Methods

Animal Studies

Adult, 10-week-old male SHR (weight, 270 to 306 g) and age-matched male Wistar-Kyoto rats (WKY), (weight, 280 to 320 g)
were purchased from Taconic Farms, Germantown, NY. The National Institute of Mental Health Animal Care and Use Committee approved all procedures.

Osmotic minipumps were implanted subcutaneously the day after arrival at the National Institute of Mental Health to deliver drugs at a constant infusion rate: candesartan (0.5 mg/kg per day for 3, 7, or 14 days), propranolol (0.5 mg/kg per day for 14 days), or vehicle (0.1N Na2CO3). The experiments were blinded to knowledge and therapy assignments. Arterial pressures in conscious rats were measured 1 day before treatment and the last day of treatment by the tail-cuff method. At 10 weeks of age, the arterial blood pressure in SHR was clearly high and had reached steady values.

Quantitative Autoradiography

Quantitative autoradiography of Ang II AT1 and AT2 receptors in brain sections was performed by incubation with 0.5×10^-9 mol/L [125I]Sar1-Ang II (2200 Ci/mmol, iodinated at New England Nuclear) (total binding), in the presence of selective AT1 (10^-6 mol/L losartan, Dupont Merck) or AT2 (10^-7 mol/L CGP 42112, Neosystems, or 10^-6 mol/L PD 123319, Parke Davis) ligands, respectively, to determine the amount of AT1 and AT2 receptors. Sections were further stained with hematoxylin-eosin for histological analysis, and structures were identified according to Paxinos and Watson.

Cerebral Blood Flow Autoregulation

We studied the upper and lower parts of the cerebral blood flow autoregulation curve in SHR and WKY anesthetized with ketamine (100 mg/kg IP) and xylazine (10 mg/kg IP) and ventilated with intratracheal intubation with 0.35% halothane and 30% oxygen. Systemic blood pressures were increased with a phenylephrine infusion or decreased by hemorrhage. Cerebral blood flow was determined with a laser-Doppler flowmetry probe (BPM2, Vasamedics, Inc).

Reversible Middle Cerebral Artery Occlusion

We performed reversible middle cerebral artery occlusions in SHR with reperfusion after 1 or 2 hours, with an intraluminal thread technique. Rats were anesthetized with 3.0% halothane and maintained with 1.0% halothane in 70% nitrous oxide and 30% oxygen under a ventilator with intratracheal intubation. We monitored cerebral blood flow by laser-Doppler flowmetry at 3 points on the surface in the affected hemisphere: point A, 1 mm from the midline and outside of the site of ischemia; point B, 3 mm from the midline and closer to the site of ischemia; and point C, 5 mm from the midline and at the periphery of the zone of ischemia (Figure 4). Ventilation was adjusted to keep blood pH between 7.35 and 7.45, PaCO2 between 32 and 40 mm Hg, and PaO2 between 130 and 180 mm Hg. Rectal temperature was maintained between 36.5°C and 37.5°C with a heating pad.

Measurement of Volume of Injury

We determined the infarct volume after 24 hours of ischemia with the 2,3,5-triphenyltetrazolium chloride (TTC) method with image scanning and computerized microdensitometry after correction for brain swelling. Cerebral edema was measured by subtracting the volume of the nonaffected hemisphere from the volume of the affected hemisphere divided by the volume of the nonaffected hemisphere.
middle cerebral artery of SHR predominantly expressed AT2 receptors (Figure 1). The decrease in AT1 receptor binding in the middle cerebral artery was 80% (results not shown). In this artery, candesartan treatment, 0.5 mg/kg per day for 14 days, decreased AT1 binding by 80% (results not shown). The reduction in AT1 receptor binding occurred approximately 10% of the total binding (results not shown).

Effects of Drug Treatments on Blood Pressure
Systolic blood pressures were measured in 6 rats of each group by the tail-cuff method. Blood pressures were significantly higher in untreated SHR compared with untreated WKY. In both WKY and SHR, systolic blood pressures were progressively decreased by treatment with candesartan 0.5 mg/kg per day. A similar decrease occurred after treatment with propranolol. After 14 days of treatment, the blood pressure in SHR was not significantly different from that of untreated WKY. Blood pressures were as follows: WKY, 124±5 and 75±5 mm Hg for control and candesartan-treated, respectively (P<0.05); SHR, 166±3, 112±3, and 116±4.5 mm Hg for control, candesartan-treated, and propranolol-treated rats, respectively (P<0.05; candesartan versus control and propranolol versus control). There was no significant difference in blood pressure between candesartan- and propranolol-treated rats.

When determined under anesthesia and basal conditions, there was a significant difference of baseline mean arterial blood pressures between untreated WKY and untreated SHR. In both WKY and SHR, treatment with 0.5 mg/kg per day candesartan significantly reduced baseline mean arterial blood pressure as early as after 3 days of treatment, and the reduction in baseline mean arterial blood pressure was more pronounced in SHR after 14 days of treatment (results not shown).

Effects of Candesartan on Cerebrovascular Autoregulation
Control SHR showed a significant shift to the right, toward higher blood pressures, compared with WKY at both the upper and the lower parts of the autoregulation curve (Figure 3B and 3C).

Treatment with candesartan significantly shifted the upper and lower limits of autoregulation in both WKY and SHR, toward the left, in the direction of lower blood pressures. The change occurred as early as after 3 days of treatment, progressed gradually with the duration of treatment, and was greater after 14 days of treatment (Figure 3A). When SHR were treated with candesartan for 14 days, there was a significant difference in both the upper and lower limits of autoregulation compared with untreated SHR controls. In SHR treated for 14 days, the lower limit of autoregulation was no longer significantly different from that of untreated WKY (Figure 3C).

Effects of Temporary Occlusion and Reperfusion of the Middle Cerebral Artery
In preliminary experiments, we determined that untreated SHR were far more sensitive to ischemia after middle cerebral artery occlusion than WKY. Because of this and the higher incidence of stroke in hypertension, we confined our studies to SHR. In a preliminary experiment in untreated SHR, we determined the course of the ischemia/reperfusion and the response of the cerebral circulation. When middle cerebral artery was occluded successfully, cerebral blood flow values did not significantly change when measured 1 mm from the midline, outside of the site of ischemia (point A on Figure 4). However, cerebral blood flow values de-
creased to <30% of baseline values when measured closer to the site of the ischemia, at point B, 3 mm from the midline, and at point C, 5 mm from the midline (Figure 4B1, 4B2, and 4C1). Both points B and C are considered to be located at the periphery of the zone of ischemia. Some animals developed subarachnoid hemorrhage or subdural hematoma, as determined by a decrease in cerebral blood flow values to <30% of baseline at point A or by a sudden cerebral blood flow reduction to <30% of baseline values at point A and absence of cerebral blood flow restoration at points B or C during reperfusion. Other animals did not develop cerebral infarction during the procedure, as determined by the restoration in cerebral blood flow to 50% of baseline values at point C, corresponding to the site of the ischemia, within 30 minutes after the occlusion. In these animals with early restoration of cerebral blood flow, cerebral infarction never occurred, as demonstrated by histological staining with TTC 24 hours after reperfusion. Rats with incomplete ischemia or subarachnoid hemorrhage (2 vehicle controls and 1 treated with candesartan) were not included in the study.

Cerebral blood flow decreased after successful middle cerebral artery occlusion. Abrupt reductions in cerebral blood flow were approximately 20% of baseline values at point A, 80% to 88% at point B, and 76% to 90% at point C. After reperfusion following either 1 or 2 hours of ischemia, cerebral blood flow at points A or B (Figure 4) was restored to values not significantly different from those before the occlusion. We did not find significant differences in cerebral blood flow between control and candesartan-pretreated rats before ischemia. Blood pH and concentrations of blood gases remained within normal limits and were similar among all groups (Table).

Cerebral blood flow decreased after successful middle cerebral artery occlusion. Abrupt reductions in cerebral blood flow were approximately 20% of baseline values at point A, 80% to 88% at point B, and 76% to 90% at point C. After reperfusion following either 1 or 2 hours of ischemia, cerebral blood flow at points A or B (Figure 4) was restored to values not significantly different from those before the occlusion.

We did not find significant differences in cerebral blood flow restoration after AT1 blockade at point A (results not shown). In our experiments, point B corresponds to the more peripheral, marginal zone of ischemia (Figure 4). At point B, pretreatment with the AT1 antagonist did not alter the initial abrupt decrease in blood flow (Figure 4B1 and 4B2). How-
ever, when animals were pretreated with candesartan, the decrease in blood flow at point B was significantly reduced 30 to 90 minutes after middle cerebral artery occlusion (Figure 4B1 and 4B2). This effect was significant when the middle cerebral artery was occluded for either 1 or 2 hours (Figure 4B1 and 4B2). Point C is an area still marginal but closer to the central core of ischemia. At point C, when submitted to ischemia for only 1 hour, there was no difference in the decrease in blood flow during ischemia between candesartan-pretreated and vehicle-treated rats (Figure 4C1). After reperfusion, candesartan-pretreated rats restored their cerebral blood flow to 112% of baseline values. In vehicle-treated rats, the blood flow at point C remained decreased to 64% of baseline values (Figure 4C1). Thus, when the middle cerebral artery was occluded for 1 hour, the cerebral blood flow was, at point C, completely restored only in candesartan-pretreated rats. Pretreatment with candesartan followed by 2 hours of ischemia and reperfusion resulted in only a partial restoration of blood flow at point C (results not shown), indicating that the effect of candesartan pretreatment was dependent on the duration of the ischemia.

Ischemia resulting from middle cerebral artery occlusion resulted in brain injury of the ipsilateral hemisphere, including cortical and subcortical (striatum-pallidum) areas, and significant ipsilateral brain edema. In the candesartan-pretreated rats submitted to 1 hour of ischemia, total (cortical plus subcortical) and cortical volumes of injury corrected for edema volume were significantly decreased by 58% and 64% relative to those in control vehicle-treated rats (Figures 5A and 5B and 6). A similar decrease in the volume of ischemia after candesartan treatment occurred when the period of ischemia was increased to 2 hours (Figure 5A through 5D). In subcortical areas, the volume of injury was not affected either by the duration of the ischemia or by pretreatment with candesartan (Figure 5C).

Brain edema was dependent on the duration of the ischemia and was significantly higher after 2 hours of ischemia compared with 1 hour of ischemia (Figure 5D). Pretreatment with candesartan decreased brain edema after 1 or 2 hours of ischemia, but the change was significant only after 2 hours of ischemia (Figure 5D).

Conversely, pretreatment with propranolol, administered at a dose that decreased blood pressure to a degree similar to that of candesartan, did not modify either the volume of ischemia or the brain edema resulting from the middle cerebral artery occlusion with reperfusion, as determined after 2 hours of ischemia (Figure 5A through 5D).

In conclusion, candesartan pretreatment reduced ischemic injury in the cortex of SHR submitted to 1 or 2 hours of ischemia and reduced brain edema in SHR submitted to 2 hours of ischemia.

Discussion

Our results demonstrate that selective antagonism of Ang II AT1 receptors by chronic peripheral administration of the AT1 antagonist candesartan normalizes cerebrovascular autoregulation and protects against brain ischemia in genetically hypertensive rats.

There is a relationship between alterations in cerebral blood flow and vulnerability to ischemia in hypertensive subjects. In genetic and experimental hypertension, cerebral
arteries are less compliant because of increased thickness with smooth muscle proliferation. This results in a shift of the cerebrovascular autoregulatory curve to the right, in the direction of higher blood pressures, with a decreased capacity for vasodilatation in the face of reduced perfusion pressures. Hypertensive subjects are predisposed to brain ischemia and stroke in part because of their decreased capacity for cerebrovascular adaptation to the reduction in blood flow during stroke.

After the initial discovery of the presence of Ang II receptors in brain arteries, we studied the effects of the AT<sub>1</sub> antagonist candesartan in cerebral blood flow autoregulation. In normotensive rats, candesartan treatment shifted the autoregulatory curve to the left. This suggested that stimulation of AT<sub>1</sub> receptors by Ang II results in a normal vasoconstrictor tone in cerebral arteries. Under resting conditions, cerebral blood flow does not change after AT<sub>1</sub> receptor blockade, probably because of a compensatory vasoconstriction of small cerebral resistance arteries. Studies on SHR revealed that acute and chronic administration of candesartan results in a normalization of the upper part of the cerebrovascular autoregulatory curve. The normalization of cerebrovascular autoregulation in SHR by chronic candesartan treatment extends to both the upper and the lower parts of the autoregulatory curve (Reference and present results) and is progressive over time, as demonstrated here. The increased capacity to vasodilate resulting from AT<sub>1</sub> blockade may be due to a decrease in the medial thickness of cerebral arteries and inhibition of the injury-related proliferation of smooth muscle, in a manner similar to that of ACE inhibitors. Thus, the normalization of cerebrovascular autoregulation by candesartan in SHR may be the result of antagonism of enhanced Ang II constrictive and growth-promoting effects in the cerebral circulation. This results in improvement of brain artery compliance with increased capacity for vasodilatation of cerebral arteries.

To establish whether the normalization of cerebrovascular flow by chronic pretreatment with candesartan was related to its protective effect against brain ischemia, we studied cerebral blood flow after stroke. During stroke, if cerebrovascular responses were normalized by AT<sub>1</sub> blockade, the capacity for vasodilatation in areas receiving collateral circulation could be improved and restored, and blood flow could be more easily maintained or recovered than in control untreated subjects. After chronic candesartan treatment, we found this to be precisely the case. Candesartan pretreatment significantly decreased the volume of ischemic injury in the cortex area in rats occluded for 1 or 2 hours. A beneficial effect of candesartan pretreatment was also demonstrated in rats submitted to 2 hours of ischemia, as evidenced by a significant decrease in cerebral edema. These effects are probably a result of higher perfusion than that of control untreated rats at the periphery of the ischemic brain lesion (points B and C, Figure 4), areas probably receiving collateral circulation from unoccluded brain arteries. During ischemia, in the periphery of the ischemic zone, blood flow is reduced to approximately 15% to 20% of preischemia values (Reference and present results). AT<sub>1</sub> blockade significantly reduced the decrease in
cerebral blood flow 30 to 90 minutes after middle cerebral artery occlusion and improved the recovery of blood flow that occurs during reperfusion in the area of penumbra, at the periphery of the ischemic lesion. This can be explained by improved capacity for vasodilatation resulting in increased collateral flow to the marginal area of ischemia. In addition, blockade of AT1 receptors could also decrease the stimulation of superoxide and peroxynitrite production by Ang II in blood vessels. Superoxide ion formation by Ang II could produce cytotoxic effects, including increases in blood-brain barrier permeability, and this may explain the decrease in cerebral edema after candesartan pretreatment.

In addition, peripheral administration of candesartan inhibits AT1 receptor binding in brain areas such as the nucleus of the solitary tract, contributing to regulate cerebrovascular flow through modulation of central sympathetic activity and in turn modulation of the brain Ang II system and in the middle cerebral artery. Chronic peripheral administration of candesartan inhibits binding to AT1 receptors to the same extent in brain areas outside and inside the blood-brain barrier, indicating that under the conditions of our experiments, candesartan readily penetrates the blood-brain barrier (Reference 29 and present experiments).

In SHR, both the central sympathetic activity and the central Ang II system are activated. Activation of the central Ang II system in SHR has been demonstrated by increased Ang II formation in the brain, increased Ang II AT1 receptor expression, and normalization of blood pressure by central administration of AT1 receptor antagonists. Central inhibition of AT1 receptors in areas regulating the sympathetic system could contribute to normalize cerebrovascular blood flow and result in additional beneficial effects.

Candesartan binds in an insurmountable fashion and was normally not washed off completely during our incubation procedures. For this reason we cannot determine whether decrease in receptor binding is due to receptor occupancy or downregulation.

Because candesartan pretreatment improves the restoration of blood flow after ischemia, we propose that normalization of cerebrovascular autoregulation by AT1 blockade is an important mechanism underlying the protective effects of candesartan.

An important question is whether the protective effects of inhibition of the Ang II system could be simply the result of the reduction in blood pressure. There is evidence that this may not necessarily be the case. The effects of AT1 blockade on cerebrovascular autoregulation are important for the improvement and restoration of blood flow during and after stroke, as reported here and as has been demonstrated not only in hypertensive but also in normotensive rats. Treatment of normotensive rats with ACE inhibitors or by brain AT1 blockade with centrally administered irbesartan improves neurological outcome after stroke, and ACE inhibitors at doses lower than those required to normalize blood pressure reduce cerebral edema in stroke-prone rats. In addition, as demonstrated here, normalization of blood pressure in SHR after treatment with propranolol does not protect from the results of ischemia. For these reasons we hypothesize that the protective effects of candesartan are not necessarily dependent on its effects on blood pressure.

The possible role of the relationship of AT1 and AT2 receptors in cerebral arteries is of interest. In vivo administration of Ang II can dilate or constrict brain arteries. It is possible that the effects of Ang II depend on a balance of stimulation of cerebrovascular AT1 and AT2 receptors. In young rats, large cerebral arteries predominantly express AT2 receptors, as determined by autoradiography. However, the number of AT2 receptors in cerebral arteries decreases with age, and in adult rats, brain vessels such as the middle cerebral artery predominantly express AT1 receptors. In adult rats the functional Ang II receptors in cerebral arteries are of the AT1 subtype, and their stimulation produces vasoconstriction, as determined in vitro. It is possible that under conditions of AT1 blockade in cerebral arteries, the cerebrovascular tone is shifted to vasodilatation, resulting in a decreased reduction of blood flow under conditions of ischemia. The possible role of brain and/or cerebrovascular AT2 receptors during brain ischemia remains an open question.

Continuous pretreatment with an AT1 antagonist such as candesartan normalized cerebral blood flow autoregulation in genetically hypertensive rats, raised the resistance against cerebral hypotension, and effectively restricted the volume of ischemic injury, resulting in the prevention of brain injury after temporary ischemia. Treatment with candesartan has been reported to decrease end-organ damage after ischemia. Our demonstration of effective and selective AT1 blockade after chronic peripheral administration of candesartan indicates that this compound may be effective as a preventive treatment of neuronal injury in clinical conditions.

It appears that the protective effects of AT1 receptor antagonism with candesartan pretreatment are likely to be related to the normalization of cerebrovascular autoregulation in the marginal ischemia zone, resulting in decreased neuronal injury. In addition, possible therapeutically beneficial effects include a normalization of blood-brain barrier permeability, which is increased during ischemia, resulting in decreased cerebral edema, and the specific inhibition of brain AT1 receptors, resulting in normalization of brain sympathetic activity, which is increased during hypertension.

The present data demonstrate an important role for Ang II in cerebrovascular control and indicate that therapeutic inhibition of the central Ang II system, and in particular pretreatment with selective AT1 receptor antagonists such as candesartan, could reduce neuronal injury resulting from cerebral ischemia.

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References
The brain can tolerate high degrees of variability in its levels of blood flow. However, sudden and massive reduction of blood flow that occurs during brain ischemia results in neuronal death at the core of the infarct. Because certain levels of cerebral blood flow are necessary to maintain neural function and cellular integrity, at the periphery of the lesion the degree of blood flow reduction can determine the development of processes leading to either survival or delayed neuronal death. Vasodilatation of collateral circulation during ischemia can reduce the loss of blood flow and allow neuronal survival, protecting brain function.

In hypertensive patients the absolute level of cerebral blood flow is similar to that in normotensive subjects. In hypertension, however, the cerebrovascular autoregulation (that is, the capacity of cerebral blood vessels to constrict or dilate in response to alterations in pressure to maintain a constant level of blood flow) is shifted toward higher pressures in the autoregulatory curve impairs the tolerance to lower perfusion rates during brain ischemia. The brain can tolerate high degrees of variability in its levels of cerebral blood flow. However, sudden and massive reduction of blood flow that occurs during brain ischemia results in neuronal death at the core of the infarct. Because certain levels of cerebral blood flow are necessary to maintain neural function and cellular integrity, at the periphery of the lesion the degree of blood flow reduction can determine the development of processes leading to either survival or delayed neuronal death. Vasodilatation of collateral circulation during ischemia can reduce the loss of blood flow and allow neuronal survival, protecting brain function.
and can make ischemic episodes in hypertension more frequent and more severe.¹

Many factors regulate cerebral blood flow. Evidence continues to accumulate indicating the involvement of angiotensin II in the regulation of the processes occurring in cerebral ischemia. Chronic inhibition of angiotensin-converting enzyme normalizes cerebrovascular autoregulation, which shifts the autoregulation curve to the left, signaling an improved capacity to vasodilate.² This led to the speculation that the normalization of blood flow that followed blockade of angiotensin II production played a central role in the reduction of the occurrence of stroke and circulatory alterations during ischemia in stroke-prone spontaneously hypertensive rats.³

The preceding study provides evidence that pretreatment with candesartan, administered peripherally, reduced the volume of cortical infarcts and the brain edema after middle cerebral artery occlusion in genetically hypertensive rats. Candesartan is a potent, insurmountable angiotensin II AT₁ receptor antagonist that gains access to the brain after peripheral administration and inhibits brain and cerebrovascular, in addition to peripheral, AT₁ receptors.⁴ Several aspects of the present study are noteworthy. Cerebral blood vessels of adult genetically hypertensive rats predominantly express the physiologically active AT₁ receptor, and candesartan blocks these receptors. The AT₁ antagonist is able to reverse the alterations in cerebrovascular autoregulation that are characteristic in genetic hypertension, shifting the autoregulatory curve toward the left, in the direction of improved vasodilation. Pretreatment with candesartan partially prevents the decrease in blood flow in the marginal zone of ischemia that is characteristic in stroke. These findings indicate that peripheral administration of candesartan results in a decrease in cerebrovascular vasoconstrictor tone and in a higher capacity of the collateral circulation to vasodilate during stroke. This is probably due to a reversal of the structural abnormalities that develop in cerebral blood vessels during chronic hypertension and to the blockade of cerebrovascular AT₁ receptors. Additional beneficial effects may be, as demonstrated here, the result of AT₁ receptor blockade in brain areas such as the nucleus of the solitary tract that contribute to regulate cerebral blood flow. Maintenance of a certain level of blood flow, crucial for neuronal survival, can explain the protective effect of candesartan during stroke. The effects of AT₁ blocker are not necessarily related to the decrease in blood pressure, because not all antihypertensive compounds offer a similar protective effect.

The present study may offer an explanation of the possible mechanism for the improved neurological outcome and reduced cFos and c-Jun expression after stroke when another AT₁ antagonist, irbesartan, is administered into the brain,⁵ and it emphasizes the possible important role of the brain and cerebrovascular angiotensin II system in the regulation of cerebral blood flow. It appears from the present results that the effects in cerebrovascular flow are important for the protective effect of AT₁ antagonism in brain ischemia.⁶ It is also possible that blockade of AT₁ receptors in selective brain areas by candesartan, as demonstrated here, could contribute to the enhanced capacity to vasodilate, through a reduction in central sympathetic tone. AT₁ receptor blockade could also enable cerebrovascular AT₂ receptors to become functionally predominant, contributing to improved capacity to vasodilate, which is an interesting and testable hypothesis that the researchers can examine.

Chronic blockade of brain and cerebrovascular AT₁ receptor partially prevents the reduction in blood flow during brain ischemia. This, in turn, could significantly decrease the cascade of receptor activation, loss of energy stores, release of excitotoxic amino acids, disintegration of membranes, activation of proteolytic enzymes, formation of free radicals, and fragmentation of DNA that lead to neuronal death and permanent loss of function.

The question remains of the possible clinical implications of the recent findings. Oral administration of AT₁ antagonists is a common antihypertensive therapy in humans. Studies are under way to determine whether long-term treatment with AT₁ antagonists such as candesartan, which gain access to the brain, can reduce the incidence and severity of stroke in hypertensive patients and whether antihypertensive medication improves cognition in the elderly.⁷ If improvement of cerebral blood flow plays a role in preventing cognitive deterioration in chronic hypertension, blockade of cerebrovascular and brain AT₁ receptors in addition to peripheral antihypertensive effects could be therapeutically advantageous.

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