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# Nitric oxide contributes to $AT_2$ but not $AT_1$ angiotensin II receptor-mediated vasodilatation of porcine pial arteries and arterioles

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**Abstract**

Angiotensin II elicits pial artery dilation by activating angiotensin $AT_1$ and angiotensin $AT_2$ receptors. This study determined if vasodilatation in response to angiotensin $AT_2$ receptor activation is due to stimulated release of nitric oxide (NO) in newborn pigs equipped with a closed cranial window. Angiotensin II ($10^{-8}$, $10^{-6}$ M) elicited pial artery dilatation that was unchanged by the NO synthase inhibitor $N\varpi$-Nitro-L-Arginine (L-NNA) ($10^{-6}$ M) (12±3 and 18±2 versus 12±3 and 21±4%). Angiotensin II was not associated with changes in artificial cerebrospinal fluid (CSF) cGMP concentration, an indicator of NO release. Similar data were obtained for the angiotensin $AT_1$ receptor agonist L 162,313. In contrast, the angiotensin $AT_2$ receptor agonist CGP 42112A ($10^{-8}$, $10^{-6}$ M) induced vasodilatation that was blocked by L-NNA (9±2 and 18±3 versus 1±1 and 1±1%). CGP 42112A dilatation was associated with elevated artificial CSF cGMP concentration (757±18, 1590±89, and 2101±116 fmol/ml) and such stimulated release was blocked by L-NNA. These data indicate that stimulated NO release contributes to angiotensin $AT_2$ but not angiotensin $AT_1$ induced vasodilatation. These data suggest that angiotensin II primarily elicits dilatation via angiotensin $AT_1$ receptor activation.


*Keywords:* Cerebral circulation; Signal transduction; Cyclic nucleotide; Nitric oxide

## 1. Introduction

Angiotensin II, like other components of the renin angiotensin system, has been shown to be locally produced and present in the brain (Daul et al., 1975; Philips, 1987). Two types of angiotensin II receptors, angiotensin $AT_1$ and angiotensin $AT_2$, have been identified, based on their differences in pharmacological and biochemical properties (Whitebread et al., 1989). The angiotensin $AT_1$ subtype is thought to mediate effects of angiotensin II in the brain that include modulation of cerebral hemodynamics, thirst, and vasopressin release (Hogarty et al., 1992). The effects of angiotensin $AT_2$ receptor activation are less well understood. Angiotensin $AT_2$ receptors are predominantly expressed in fetal tissue and in the brains of newborns, but are less prominent in adult tissue (Grady et al., 1991). In the newborn pig, angiotensin II and the selective angiotensin $AT_2$ receptor agonist ($N_\alpha$-Nicotinoyl-Tyr-($N_\alpha$-CBZ-Arg)-Lys-His-Pro-Ile) (CGP 42112A) (Whitebread et al., 1991) have been shown to elicit pial artery dilatation (Baranov and Armstead, 2002). Angiotensin II elicited vasodilatation that was associated with an increased cerebrospinal fluid (CSF) concentration of 6-keto prostaglandin (PG)$F_{1\alpha}$, the stable breakdown product of $PGI_2$, indicating that dilator prostaglandins contributed to the vascular response (Baranov and Armstead, 2002). Nonetheless, vasodilatation to the angiotensin $AT_2$ receptor agonist CGP 42112A was observed to be independent of prostaglandin release (Baranov and Armstead, 2002). In those studies, a selective angiotensin $AT_1$ receptor agonist had not been used and it had been concluded, by inference, that angiotensin II must primarily activate the angiotensin $AT_1$ receptor to release prostaglandins and produce vasodilatation.

Relaxation of blood vessels can be mediated by several mechanisms, including those involving cGMP, cAMP, and $K^+$ channels (Faraci and Heistad, 1998). Nitric oxide (NO) elicits dilation via cGMP and is an important contributor to the regulation of the cerebral circulation (Faraci and Heistad, 1998). While prostaglandins have been observed to elicit dilation via

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both cAMP and cGMP dependent pathways in the newborn pig cerebral circulation (Armstead, 1996), prostaglandins have historically been thought to elicit vasodilatation primarily due to a cAMP dependent mechanism. Since angiotensin $AT_2$ agonist induced vasodilatation is independent of prostaglandin release, the vascular response to activation of this angiotensin II receptor subtype could be due to NO and cGMP.

Therefore, this study determined if stimulated release of NO contributes to dilatation to activation of the angiotensin $AT_2$ receptor in the piglet cerebral circulation. This study also used a selective angiotensin $AT_1$ receptor agonist ((5,7-Dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl)imidazo[4,5,6]pyridine (L 162,313) (Vianello et al., 1998) in addition to angiotensin II to more rigorously investigate the relationship between angiotensin II receptor subtype and NO. The study design used an approach in which vascular responses to angiotensin II, L 162,313, and CGP 42112A were obtained before and after treatment with the NO synthase inhibitor *N*ω-Nitro-L-Arginine (L-NNA) and CSF samples collected for determination of cGMP concentration via radioimmunoassay (RIA). To confirm specificity of angiotensin II receptor subtype activation, responses to angiotensin II, L 162, 313, and CGP 42112A were obtained before and after the respective angiotensin $AT_1$ and angiotensin $AT_2$ receptor antagonists 5,7-Diethyl-3,4-dihydro-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl)methyl)-1,6-naphyridin-2 (1H)-one (ZD 7155) (Junggren et al., 1996) and *S*(+)-1-[[4-(Dimethylamino)-3-methylphenyl]methyl]-5-diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-*c*]pyridine-6-carboxylic acid (PD 123,319) (Blankley et al., 1991).

## 2. Materials and methods

Newborn pigs (1–5 days old, 1.2–1.6 kg) of either sex were used in these experiments. All protocols were approved by the Institutional Animal Care and Use Committee. Animals were sedated with isoflurane (1–2 MAC). Anesthesia was maintained with a-chloralose (30–50 mg/kg. supplemented with 5 mg/kg/h i.v.). A catheter was inserted into a femoral artery to monitor blood pressure and to sample for blood gas tensions and pH. Drugs to maintain anesthesia were administered through a second catheter placed in a femoral vein. The trachea was cannulated, and the animals were mechanically ventilated with room air. A heating pad was used to maintain the animals at 37–39 °C, monitored rectally.

A cranial window was placed in the parietal skull of these anesthetized animals. This window consisted of three parts: a stainless steel ring, a circular glass coverslip, and three ports consisting of 17-gauge hypodermic needles attached to three precut holes in the stainless steel ring. For placement, the dura was cut and retracted over the cut bone edge. The cranial window was placed in the opening and cemented in place with dental acrylic. The volume under the window was filled with a solution, similar to CSF, of the following composition (in mM): 3.0 KCl, 1.5 $MgCl_2$, 1.5 $CaCl_2$, 132 NaCl, 6.6 urea, 3.7 dextrose, and 24.6 $NaHCO_3$. This artificial CSF was warmed to 37 °C and had the following chemistry: pH 7.33, $p_{CO_2}$ 46 mm Hg, and $p_{O_2}$ 43 mm Hg, which was similar to that of endogenous CSF. Pial arterial vessels were observed with a dissecting microscope, a television camera mounted on the microscope, and a video output screen. Vascular diameter was measured with a video microscaler.

### 2.1. Protocol

Two types of pial vessels, small arteries (resting diameter, 120–160 μm) and arterioles (resting diameter, 50–70 μm) were examined to determine whether segmental differences in the effects of AII agonists could be identified. Typically, 2–3 ml of artificial CSF were flushed through the window over a 30s period, and excess CSF was allowed to run off through one of the needle ports. For sample collection, 300 μl of the total cranial window volume of 500 μl was collected by slowly infusing artificial CSF into one side of the window and allowing the CSF to drip freely into a collection tube on the opposite side.

Four types of experiments were performed: 1) sham control ($n=9$), 2) L-NNA treated ($n=9$), 3) ZD 7155 treated ($n=5$) and 4) PD 123,319 treated ($n=5$). In sham control experiments, responses to topical angiotensin II, L 162,313, and CGP 42112A ($1\times10^{-8}$, $1\times10^{-6}$ M) were obtained initially and then again 60 min later to determine if responses were reproducible over time. In the second group of experiments, responses to angiotensin II, L 162,313 and CGP 42112A were obtained initially and then again 60 min after topical administration of L-NNA ($1\times10^{-6}$ M). Similarly, in the third and fourth group of experiments, responses to angiotensin II, L 162,313, and CGP 42112A were obtained initially and then again 60 min after topical administration of either ZD 7155 ($1\times10^{-6}$ M) or PD 123, 319 ($1\times10^{-6}$ M). In the latter three groups of animals, the antagonist was co-administered with each of the agonists during the generation of dose response curves so as to maintain continued exposure to the respective antagonist. Because baseline artery diameter changed as a result of L-NNA administration, data were calculated as the percent change from baseline to normalize such differences.

### 2.2. RIA analysis of artificial CSF cGMP concentration

Artificial CSF samples collected after a 10-min exposure to an agent were analyzed for cGMP concentration using scintillation proximity assay methods. Commercially available kits for cGMP (Amersham) were used. Briefly, this assay determines cyclic nucleotide concentration for binding to an antiserum that has a high specificity for the cyclic nucleotide. The antibody-bound cyclic nucleotide is then reacted with an anti-rabbit second antibody bound to fluoromicrospheres. Labeled cyclic nucleotide bound to the primary rabbit antibody can then be measured by determining the amount of light emitted by the fluoromicrospheres. All unknowns were assayed at two dilutions, with the lower limit of detection being 100 fmol/ml. The concentration of the unlabeled cyclic nucleotide is calculated from the standard curve via linear regression analysis.

### 2.3. Statistical analysis

Pial artery diameter, artificial CSF cGMP, and systemic arterial pressure values were analyzed using ANOVA for repeated measures. If the value was significant, the data were then analyzed by Fishers protected least significant difference test. An α level of $P<0.05$ was considered significant in all statistical tests. Values are represented as mean±S.E.M of the absolute value or as percentage changes from control values.

## 3. Results

### 3.1. Role of NO in pial artery dilatation to angiotensin II, L 162,313, and CGP 42112A

Topical angiotensin II, L 162,313, and CGP 42112A ($1\times10^{-8}$, $1\times10^{-6}$ M) elicited reproducible pial small artery (120–160 μm) and arteriole (50–70 μm) vasodilatation (data not shown). Vascular responses to CGP 42112A were associated with an increase in the concentration of cGMP in cortical periarachnoid artificial CSF (Fig. 1). However, no such change in CSF cGMP was observed after the administration of either angiotensin II or L 162,313 (Fig. 1). Topical L-NNA ($1\times10^{-6}$ M) decreased baseline CSF cGMP concentration and blocked stimulated release of cGMP by CGP 42112A (Fig. 1).

Pial small artery dilatation to CGP 42112A was blocked by L-NNA administration (Fig. 2). However, vascular responses to AII and L 162,313 were unchanged after L-NNA (Fig. 2). Similar effects were observed in pial arterioles.

### 3.2. Influence of ZD 7155 and PD 123,319 on pial artery dilatation to angiotensin II, L 162,313, and CGP 42112A

The angiotensin $AT_1$ receptor antagonist ZD 7155 ($1\times10^{-6}$ M) markedly reduced pial small artery dilatation to angiotensin II and L 162,313 while responses to CGP 42112A were unchanged (Fig. 3). Conversely, responses to CGP 42112A were

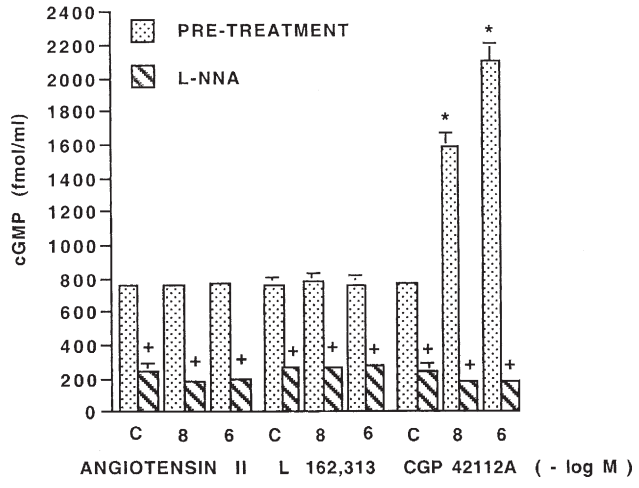


Fig. 1. Influence of topical angiotensin II, L 162,313, and CGP 42112A ($1\times10^{-8}$, $1\times10^{-6}$ M) on CSF cGMP (fmol/ml) before (pre-treatment) and after topical L-NNA ($1\times10^{-6}$ M), $n=9$. $^{*}P<0.05$ versus corresponding control value (c). $^{+}P<0.05$ versus corresponding pre-treatment value.

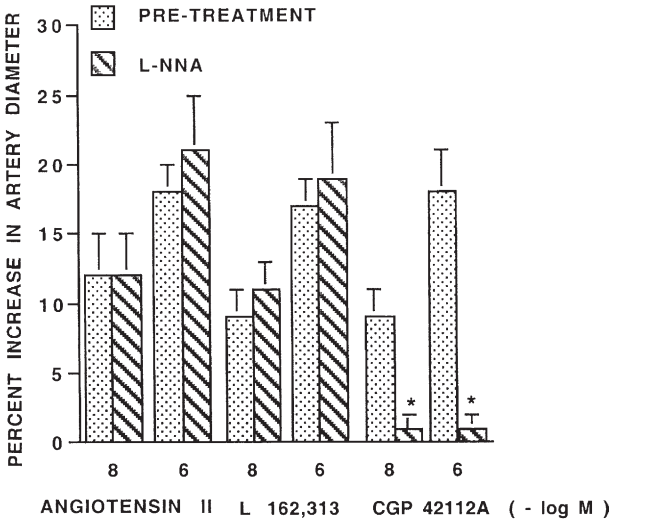


Fig. 2. Influence of topical angiotensin II, L 162,313, and CGP 42112A ($1\times10^{-8}$, $1\times10^{-6}$ M) on pial small artery diameter before (pre-treatment) and after topical L-NNA ($1\times10^{-6}$ M), $n=9$. $^{*}P<0.05$ versus corresponding pre-treatment value.

markedly reduced by the angiotensin $AT_2$ antagonist PD 123,319 while responses to L 162,313 were unchanged (Fig. 3). Administration of PD 123,319 attenuated the vascular response to the higher concentration of angiotensin II ($1\times10^{-6}$ M), but responses to the lower concentration ($1\times10^{-8}$ M) were unchanged (Fig. 3). Similar data were obtained in pial arterioles.

### 3.3. Influence of L-NNA, ZD 7155, and PD 123,319 on pial artery diameter

L-NNA decreased pial small artery and arteriole diameter (153±9 versus 125±6 μm for pial small arteries). ZD 7155 and

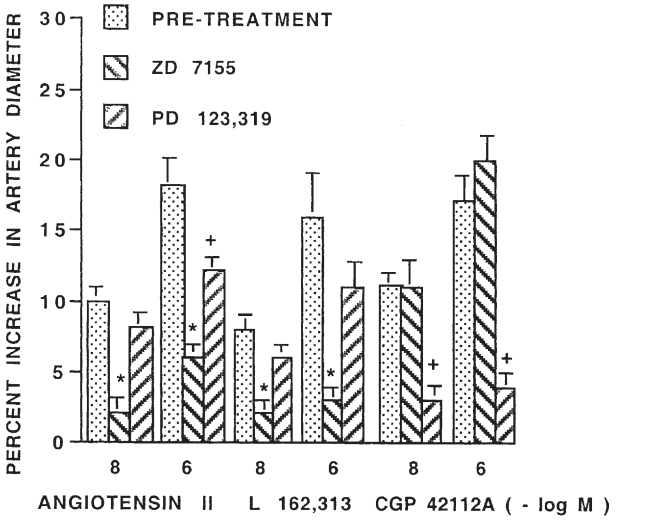


Fig. 3. Influence of topical angiotensin II, L 162,313, and CGP 42112A ($1\times10^{-8}$, $1\times10^{-6}$ M) on pial small artery diameter before (pre-treatment) and after either topical co-administered ZD 7155 ($1\times10^{-6}$ M) or PD 123,319 ($1\times10^{-6}$ M), $n=5$. Data for angiotensin II and CGP 42112A from Baranov and Armstead (2002). $^{*}P<0.05$ versus corresponding pre-treatment value in ZD 7155 treated animals $^{+}P<0.05$ versus corresponding pre-treatment value in PD 123,319 treated animals.

PD 123,319 had no significant effect on pial small artery or arteriole diameter.

### 3.4. Blood chemistry

Blood chemistry and mean arterial blood pressure values were collected at the beginning and at the end of all experiments. There were no significant differences in the values for pH, $p_{CO_2}$, $p_{O_2}$, or mean arterial blood pressure either within or between experimental groups.

## 4. Discussion

Results of the present study show that angiotensin II, and the purported selective angiotensin $AT_1$ and angiotensin $AT_2$ receptor agonists L 162,313 and CGP 42112A (Vianello et al., 1998; Whitebread et al., 1991) elicited concentration dependent increases in pial artery diameter. Increases in pial artery diameter in response to CGP 42112A were accompanied by increased cortical periarachnoid CSF cGMP concentration while CSF cGMP concentration was unchanged after angiotensin II and L 162,313 administration. Symmetrically, vascular responses to CGP 42112A were blocked by the administration of the NO synthase inhibitor L-NNA while vasodilator responses to angiotensin II and L 162,313 were unchanged. These data indicate that the biochemical data support and corroborate the pharmacological data to show that NO contributes to pial artery vasodilatation in response to angiotensin $AT_2$ but not angiotensin $AT_1$ receptor activation. Since data obtained were no different in pial small arteries versus that in pial arterioles, these observations suggest that there are minimal differences in the role of NO in the mediation of dilation to angiotensin $AT_2$ subtype activation as a function of resistance vessel size. The inability of L-NNA to affect angiotensin II and L 162,313 vasodilatation most probably did not, however, relate to an inability to block NO/cGMP actions. For example, the concentration of L-NNA used in this study has previously been observed to decrease resting CSF cGMP concentration and elicit pial artery constriction (Armstead, 1995). Additionally, L-NNA blocked dilation to the NO dependent dilator substance P, while responses to the NO releaser sodium nitroprusside were unchanged (Armstead, 1998), further indicating that this agent was an efficacious and selective NO synthase inhibitor. Further, using the quantification of conversion of [$^{14}$C]-citrulline from [$^{14}$C]-arginine as an index of NO synthase activity, it was observed that NO synthase activity in the cerebral cortex was decreased by 79% using such an L-NNA concentration (Armstead, 1998).

Additional results of the present study support the use of L 162,313 and CGP 42112A as selective angiotensin $AT_1$ and angiotensin $AT_2$ receptor agonists, respectively. For example, the angiotensin $AT_2$ antagonist PD 123,319 (Blankley et al., 1991) blocked the pial artery dilation to CGP 42112A while the angiotensin $AT_1$ receptor antagonist ZD 7155 (Junggren et al., 1996) did not affect dilation to CGP 42112A, similar to that previously reported (Baranov and Armstead, 2002). Neither PD 123,319 nor ZD 7155 affects pial artery dilation to papaverine, supportive of the use of these agents as selective angiotensin II receptor subtype antagonists (Baranov and Armstead, 2002). These are the first data to demonstrate the cerebrovascular activity of the angiotensin $AT_1$ agonist, L 162,313. New data also show that dilation to L 162,313 was blocked by ZD 7155 but unchanged by PD 123,319, suggesting that this agent was a selective angiotensin $AT_1$ receptor agonist. Angiotensin II elicited dilation that was blunted by ZD 7155 at all concentrations but PD 123,319 attenuated angiotensin II dilation only at the higher agonist concentration, similar to previous observations (Baranov and Armstead, 2002). These data suggest that angiotensin II predominantly activates the angiotensin $AT_1$ receptor to elicit pial artery dilation, but can activate the angiotensin $AT_2$ receptor at high concentrations, as shown previously (Baranov and Armstead, 2002). CSF angiotensin II concentration increases to beyond $10^{-8}$ M following fluid percussion brain injury in the piglet (Baranov and Armstead, 2002), while blockade of the angiotensin $AT_1$ receptor improves impaired cerebral hemodynamics after brain injury in the piglet (Baranov and Armstead, 2003). Angiotensin II interaction with the angiotensin $AT_1$ receptor at physiologic but interaction with both angiotensin$AT_1$ and angiotensin $AT_2$ receptors at pathologic concentrations may suggest a protective role for the angiotensin $AT_2$ receptor under brain injury conditions.

In the cerebral circulation, angiotensin II displays both vasoconstricting and vasodilating activities. Some reports indicate that regionally infused or topically applied angiotensin II results in cerebral vasoconstriction in rabbits (Reynier-Rebuffel et al., 1983), hamsters (Joyner et al., 1988) and cats (Mayhan et al., 1988; Wei et al., 1978). Conversely, others reported that angiotensin II elicits moderate pial vasodilation in the newborn pig (Meng and Busija, 1993), rabbit (Haberl et al., 1991), and rat (Haberl et al., 1990). Some of these reports also suggest that angiotensin II produced vasodilation is mediated by the release of $PGI_2$ (Baranov and Armstead, 2002) and showed that administration of the cyclooxygenase inhibitor indomethacin attenuated or blocked the angiotensin II cerebral vasodilation (Haberl et al., 1991; Meng and Busija, 1993). Recent studies also showed that angiotensin $AT_1$ receptor mediated pial artery dilation was due to the release of dilator prostaglandins in the piglet, though prostaglandins did not participate in the dilation to angiotensin $AT_2$ receptor activation (Baranov and Armstead, 2002).

The role of the endothelium and cyclic nucleotides in angiotensin II and angiotensin II receptor subtype induced vasodilatation has also been an area of active research interest. For example, in rat cerebral arterioles angiotensin II induces endothelium dependent vasodilation (Haberl et al., 1990) while in rat carotid arteries, angiotensin II increased release of NO and cGMP production via endothelial angiotensin $AT_1$ receptors (Boulanger et al., 1995; Caputo et al., 1995). In the peripheral circulation, evidence supportive of angiotensin $AT_2$ receptor mediated dilation and release of cGMP and NO has been accumulated (Gohlke et al., 1998; Siragy and Carey, 1996). Nonetheless, the relationship between NO/cGMP and angiotensin $AT_2$ receptor mediated dilation has not been rigorously investigated in the cerebral circulation. Using a

pharmacologic approach, results of the present study are the first to show that angiotensin $AT_2$ receptor mediated cerebrovasodilation is NO dependent while angiotensin $AT_1$ mediated cerebrovasodilation is independent of an NO mechanism. Taken together with the results of our previous study (Baranov and Armstead, 2002), these data suggest that angiotensin II primarily elicits dilation via release of dilator prostaglandins (and presumably cAMP) at lower physiological concentrations, but produces dilation at higher pathological concentrations both via the stimulated release of NO/cGMP as well as the aforementioned release of prostaglandins. Reasons for differences between the present results and that of Boulanger et al. (1995), particularly regarding their observation that angiotensin II releases NO/cGMP via activation of the angiotensin $AT_1$ receptor, are uncertain but could relate to differences between resistance and conduit vessels, age, and/or species differences.

In conclusion, results of the present study show that stimulated NO release contributes to angiotensin $AT_2$ but not to angiotensin $AT_1$ receptor mediated cerebrovasodilatation. This study is the first to demonstrate that L 162,313 is a selective angiotensin $AT_1$ receptor agonist which elicits cerebrovasodilatation. These data suggest that angiotensin II primarily elicits dilatation via activation of the angiotensin $AT_1$ receptor.

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