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Angiotensin II-induced drinking and pressor responses to central or systemic irbesartan and losartan

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Abstract

Angiotensin II (ANG II) is a peptide hormone that is important for maintaining blood pressure and body fluid homeostasis. Two nonpeptide angiotensin type 1 (AT_1) receptor antagonists, irbesartan and losartan, were compared for their antidipsogenic and antihypertensive efficacy in both normotensive and hypertensive rats. ANG II-induced drinking and pressor responses were examined following central or systemic administration of irbesartan and losartan. Both agents inhibited the drinking response to ANG II in normotensive rats. Irbesartan was more effective than losartan at inhibiting pressor responses to ANG II in normotensive and hypertensive rats. These data indicate that centrally administered irbesartan may be somewhat more effective as an AT_1 receptor antagonist than losartan. However, evaluating the antihypertensive efficacy of these drugs when administered systemically is complex due to several pharmacokinetic factors (e.g., metabolism and lipophilicity). © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Angiotensin II; AT_1 receptor antagonists; Blood pressure; Drinking; Irbesartan; Losartan; Spontaneously hypertensive rat

1. Introduction

Body fluid homeostasis is regulated by both central and peripheral mechanisms. The peptide hormone angiotensin II (ANG II) is influential in the maintenance of blood pressure and fluid balance. ANG II is involved in the control of blood pressure through peripheral effects, such as vasoconstriction and stimulation of aldosterone secretion, and through central actions by increasing sympathetic nerve activity, inhibiting baroreflexes, and stimulating vasopressin release and salt and water intake (Johnson and Thunhorst, 1997; Phillips, 1987; Polidori et al., 1998; Song et al., 1991; Thunhorst and Johnson, 1994).

ANG II-responsive neurons and ANG II-containing nuclei have been located both within and outside of the blood–brain barrier (Song et al., 1991). Due to the limited bioavailability and therefore therapeutic utility of peptidergic angiotensin receptor antagonists, specific nonpeptide ANG II receptor antagonists have been recently developed for the treatment of hypertension. Irbesartan (2-*n*-butyl-3-[(2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl) methyl]-1,3-diaza-spiro[4,4]non) and losartan (2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*-tetrazol-5-yl)bi-phenyl-4-yl)methyl] imidazole, potassium salt) are nonpeptide angiotensin receptor antagonists that bind selectively to angiotensin type 1 (AT_1) receptors (Cazaubon et al., 1993; Chiu et al., 1990; Timmermans et al., 1993). Irbesartan is shown to bind noncompetitively to the AT_1 receptor subtype (Brunner, 1997), while losartan is a competitive antagonist (Wong et al., 1990). These compounds have similar bioavailabilities to peripheral sites when administered systemically (Cazaubon et al., 1993) and are orally active antihypertensive agents (Wong et al., 1990).

Although both irbesartan and losartan are presently used as treatments for hypertension, the specific mechanisms by which these drugs exert their antihypertensive actions are debated. Irbesartan is more lipophilic than losartan (Culman et al., 1999) and possesses roughly a 10-fold higher affinity for the AT_1 receptor (Cazaubon et al., 1993). However, losartan generates an active metabolite, EXP 3174, which increases its potency. Irbesartan has greater potency than losartan in vitro (in rat liver membranes and rabbit aorta) and in vivo on attenuating ANG II-induced pressor

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responses in monkeys and dogs (Cazaubon et al., 1993). In contrast, these drugs are similar in their ability to inhibit ANG II-induced pressor responses in rats (Cazaubon et al., 1993). Previous data are also inconsistent regarding the ability of these substances to cross the blood–brain barrier. For example, there is conflicting evidence concerning the effectiveness with which systemically administered losartan enters the central nervous system (Fregly and Rowland, 1991; Li et al., 1993; Wong et al., 1990).

Given the inconsistency of data regarding the relative efficacy with which irbesartan and losartan exert their antihypertensive effects, the purpose of the present study was to examine the ability of these two agents to attenuate ANG II-induced pressor responses and water consumption in rats, following either central or systemic administration. Both normotensive and hypertensive rats were used in the current experiments. In Sprague–Dawley rats, ANG II-induced dipsogenic and pressor responses were examined following intracerebroventricularly (icv) and intravenously (iv) administered irbesartan and losartan. In spontaneously hypertensive (SHR) and Wistar Kyoto (WKY) rats, the ability of intracerebroventricularly administered antagonists to attenuate ANG II-induced pressor responses was investigated.

2. Methods

2.1. Subjects

Male Sprague–Dawley (Harlan, Indianapolis, IN), SHR (Taconic Farms, Germantown, NY; Colony IBU-3), and WKY (Taconic Farms; Colony IBU-3) rats weighing 300–400 g were used. The animals were housed in individual, suspended wire cages. Food (Purina Rat Chow 5012) and water were available ad libitum for the duration of the experiments. The temperature was maintained at 22±2 °C. The light cycle was held at 12:12, with lights on at 06:00 h. All experiments were conducted during the light period, between 10:00 and 16:00 h.

2.2. Instrumentation and surgical procedures

2.2.1. Cerebral cannula

A cannula was implanted into the left lateral ventricle, using procedures described elsewhere (Menani and Johnson, 1995). The head was leveled between bregma and lambda. The coordinates used for a lateral ventricle cannula were 1.2 mm caudal to bregma, 1.5 mm lateral to midline, and 4.0 mm below dura mater. Rats recovered from surgery for a minimum of 5 days before the beginning of testing.

2.2.2. Vascular catheters

Rats were instrumented with vascular catheters under an Equithesin-like anesthetic cocktail (0.97-g sodium pentobarbital and 4.25-g chloral hydrate/100 ml distilled water; prepared by University of Iowa Hospitals and Clinics Pharmacy; 0.33 ml/100 g bw) (Gandal, 1969). PE-10 tubing joined to PE-50 tubing was inserted into the aorta and abdominal vena cava via the femoral artery and vein. The distal portions of the catheters were tunneled subcutaneously and externalized at the dorsal cervical region. Catheters were filled with heparinized saline (200 u/ml) and plugged with 23-G obturators. Rats recovered from surgery for a minimum of 24 h before the beginning of testing.

2.3. Central and peripheral drug injections

ANG II was purchased from Sigma (St. Louis, MO) and dissolved in saline (0.15-M NaCl) at 20 ng/2 μl. ANG II was injected into the lateral ventricles at 2 μl/kg. Losartan (purchased from DuPont, Wilmington, DE) and irbesartan (a gift from Bristol-Myers Squibb, Princeton, NJ) were dissolved in dimethyl sulfoxide at 1 μg/2 μl for Experiments 1 and 3, 3 mg/0.5 ml for Experiments 2 and 4, and 100 μg/2 μl for Experiment 5.

2.4. Water intake

Fluid intake was measured by placing the animal into a test cage, without access to food. Each subject was removed from the cage, an injector attached to a 10-μl syringe was inserted into the intracerebroventricular cannula, and the animal was returned to its cage. The dipsogen was delivered after a short habituation period. Water intake was measured by allowing the animal to drink from a modified chemical burette (0.1-ml division) placed directly on the test cage.

2.5. Arterial pressure recordings

Direct mean arterial pressure (MAP) was recorded in unanesthetized and unrestrained rats. The animal was removed from the home cage and placed in a test cage, without access to food or water. The previously implanted catheter was connected to a custom-designed pressure transducer coupled to an amplifier (University of Iowa, Iowa City, IA) and a multichannel recorder (Science Park, Cambridge, England). The analog signal was converted into digital information using Spike 2 (Cambridge Electronic Design, Cambridge, England). This program permits the acquisition of cardiovascular data by computer.

2.6. Experimental procedures

2.6.1. Experiment 1: ANG II-induced water intake following intracerebroventricular antagonist or vehicle in Sprague–Dawley rats

Eighteen Sprague–Dawley rats were instrumented with a lateral ventricle cannula. Following a recovery period of at least 5 days, animals were randomly assigned to one of three treatment conditions: vehicle ($n=6$), irbesartan

($n=6$), or losartan ($n=6$). Animals were removed from their home cages and placed into the test cages. Antagonist (1 μg/2 μl/kg) or vehicle (2 μl/kg) pretreatments were administered intracerebroventricularly. Fifteen minutes following the drug injections, ANG II (20 ng/2 μl/kg) was administered intracerebroventricularly. Water intake (ml) was recorded at 0, 15, 30, and 60 min following ANG II administration.

2.6.2. Experiment 2: ANG II-induced water intake following intravenous antagonist or vehicle in Sprague–Dawley rats

Twenty-five rats were each instrumented with a lateral ventricle cannula and a femoral vein catheter. After recovery periods of not less than 5 days and 24 h following the cannula and catheter instrumentation, respectively, each animal was administered a drinking test for each of the three treatment conditions (vehicle, irbesartan, and losartan). At least 2 days separated each drinking test, and the order of treatment was randomized.

For each drinking test, animals were removed from their home cages and placed into the test cages. Pretreatment with an antagonist (3 mg/0.5 ml/kg) or vehicle (0.5 ml/kg) was administered intravenously. Thirty minutes following the drug injections, ANG II (20 ng/2 μl/kg) was administered intracerebroventricularly. Water intake (ml) was recorded at 0, 15, 30, and 60 min following ANG II administration.

2.6.3. Experiment 3: ANG II-induced blood pressure changes following intracerebroventricular antagonist or vehicle in Sprague–Dawley rats

Ninety rats were instrumented with a lateral ventricle cannula and a femoral artery catheter. After minimum recovery periods of 5 days and 24 h following the cannula and catheter instrumentation, respectively, animals were randomly divided into three treatment conditions: vehicle ($n=24$), irbesartan ($n=33$), or losartan ($n=33$). Animals were removed from their home cages and placed into the test cages. A baseline measure of MAP (mmHg) was recorded continuously for a period of 10 min. Pretreatment with an antagonist (1 μg/2 μl/kg) or vehicle (2 μl/kg) was administered intracerebroventricularly. Thirty minutes following the drug injections, ANG II (20 ng/2 μl/kg) was administered intracerebroventricularly. MAP was recorded continuously for 10 min following ANG II administration.

2.6.4. Experiment 4: ANG II-induced blood pressure changes following intravenous antagonist or vehicle in Sprague–Dawley rats

Seventeen rats were instrumented with a lateral ventricle cannula, a femoral artery catheter, and a femoral vein catheter. After recovery periods of at least 5 days and 24 h following the cannula and catheter instrumentation, respectively, pressor responses to ANG II were measured following each of the three treatment conditions (vehicle, irbesartan, and losartan). At least 2 days separated each blood pressure test, and the order of treatment was randomized.

For each blood pressure test, animals were removed from their home cages and placed into the test cages. A baseline measure of MAP (mmHg) was recorded continuously for a period of 10 min. Pretreatment with an antagonist (3 mg/0.5 ml/kg) or vehicle (0.5 ml/kg) was administered intravenously. Thirty minutes following the drug injections, ANG II (20 ng/2 μl/kg) was administered intracerebroventricularly. MAP was measured continuously for 10 min following ANG II administration.

2.6.5. Experiment 5: ANG II-induced blood pressure changes following intracerebroventricular antagonist or vehicle in SHR and WKY

Twenty-eight rats (14 SHR and 14 WKY) were instrumented with a lateral ventricle cannula and a femoral artery catheter. After recovery periods of not less than 5 days and 24 h following the cannula and catheter instrumentation, respectively, animals were randomly divided into three treatment conditions: vehicle ($n=5$ SHR and 5 WKY), irbesartan ($n=5$ SHR and 5 WKY), or losartan ($n=4$ SHR and 4 WKY). Animals were removed from their home cages and placed into the test cages. A baseline measure of MAP (mmHg) was recorded continuously for a period of 10 min. Pretreatment with an antagonist (100 μg/2 μl/kg) or vehicle (2 μl/kg) was administered intracerebroventricularly. Thirty minutes following the drug injections, ANG II (20 ng/2 μl/kg) was administered intracerebroventricularly. MAP was recorded continuously for 10 min following ANG II administration.

2.7. Data analysis

The data are presented as means ± standard error of the mean (S.E.M.) for the indicated experiments. Statistical analyses were performed with independent-groups analyses of variance (ANOVA) for Experiments 1 and 3, repeated-measures ANOVAs for Experiments 2 and 4, and mixed-design ANOVAs for Experiment 5. Student's *t* tests (using a Bonferroni correction for multiple comparisons) were conducted to determine specific differences. A probability level of $P<.05$ was considered to be statistically significant.

3. Results

3.1. Experiment 1: ANG II-induced water intake in response to intracerebroventricular antagonist or vehicle in Sprague–Dawley rats

The drinking response to intracerebroventricular ANG II (20 ng/2 μl/kg) following intracerebroventricular antagonist (1 μg/2 μl/kg) or vehicle pretreatment was examined 60 min post-ANG II. Fig. 1 shows the results of the drinking tests. Animals consumed 3.6 ± 1.2 ml of water following vehicle pretreatment, while animals pretreated with irbesartan and losartan drank 0.1 ± 0.1 and 0.6 ± 0.4 ml, respectively. A

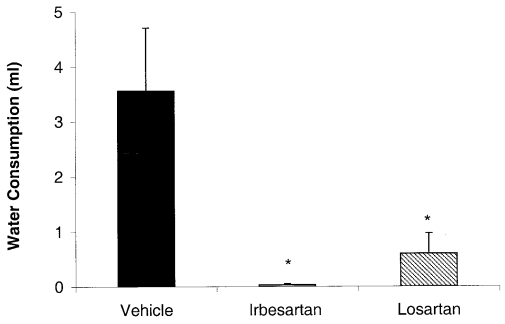

Fig. 1. Effects of intracerebroventricular administration of vehicle or antagonist (1 μg/2 μl/kg) and intracerebroventricular ANG II (20 ng/2 μl/kg) on water intake in normotensive rats. Values are expressed as means ± S.E.M. * $P < .05$ vs. vehicle.

main effect of treatment was found [$F(2,15) = 4.74$, $P < .05$]. A priori t tests (with a Bonferroni correction for multiple comparisons) demonstrated significant differences between both vehicle and irbesartan [$t(10) = 2.47$, $P < .05$] and vehicle and losartan [$t(10) = 1.52$, $P < .05$]. No difference in water intake was found between irbesartan and losartan ($P > .05$).

3.2. Experiment 2: ANG II-induced water intake in response to intravenous antagonist or vehicle in Sprague–Dawley rats

The drinking response to intracerebroventricular ANG II (20 ng/2 μl/kg) following intravenous antagonist (3 mg/0.5 ml/kg) or vehicle pretreatment was examined 60 min post-ANG II. Fig. 2 presents the results of the drinking tests. Animals consumed 7.1 ± 0.1 ml of water following vehicle pretreatment, while irbesartan- and losartan-treated animals drank 3.2 ± 0.6 and 4.6 ± 0.6 ml, respectively. The ANOVA yielded a significant main effect of treatment [$F(2,72) = 4.96$, $P < .05$]. Significant differences were found between both vehicle and irbesartan [$t(24) = 3.59$, $P < .05$] and vehicle and losartan [$t(24) = 1.81$, $P < .05$]. There was no difference in water intake between the irbesartan and losartan pretreatments ($P > .05$).

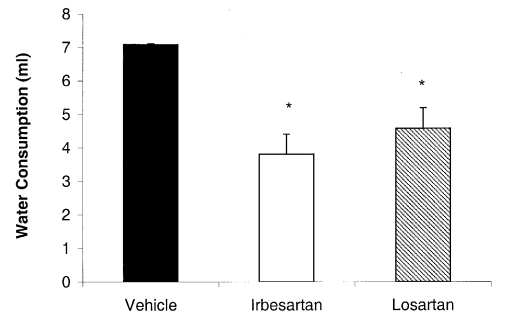

Fig. 2. Effects of intravenous administration of vehicle or antagonist (3 mg/0.5 ml/kg) and intracerebroventricular ANG II (20 ng/2 μl/kg) on water intake in normotensive rats. Values are expressed as means ± S.E.M. * $P < .05$ vs. vehicle.

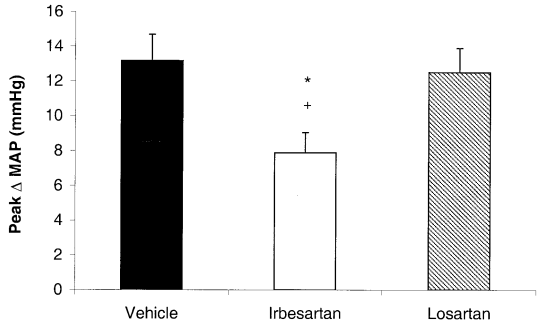

Fig. 3. Effects of intracerebroventricular administration of vehicle or antagonist (1 μg/2 μl/kg) on peak intracerebroventricular ANG II-induced (20 ng/2 μl/kg) pressor responses in normotensive rats. Values are expressed as means ± S.E.M. * $P < .05$ vs. vehicle. $^{+}P < .05$ vs. losartan.

3.3. Experiment 3: ANG II-induced blood pressure changes following intracerebroventricular antagonist or vehicle in Sprague–Dawley rats

The peak pressor response to intracerebroventricular ANG II (20 ng/2 μl/kg), compared to baseline, was examined following intracerebroventricular antagonist (1 μg/2 μl/kg) or vehicle pretreatment. Fig. 3 presents the results of the pressor tests. The peak increase in MAP for the vehicle group was 13 ± 2 mmHg, while irbesartan and losartan peak increases were 8 ± 1 and 13 ± 1 mmHg, respectively. A significant main effect of group was found [$F(2,87) = 5.58$, $P < .05$]. Significant differences were found between vehicle and irbesartan [$t(55) = 2.82$, $P < .05$] and between irbesartan and losartan [$t(64) = 2.56$, $P < .05$]. Blood pressure in vehicle and losartan groups did not differ ($P > .05$).

3.4. Experiment 4: ANG II-induced blood pressure changes following intravenous antagonist or vehicle in Sprague–Dawley rats

The peak pressor response to intracerebroventricular ANG II (20 ng/2 μl/kg), compared to baseline, was exam-

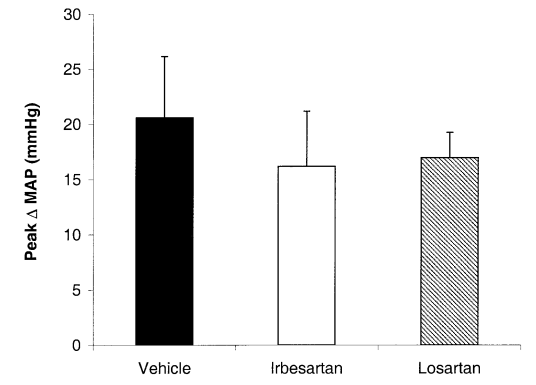

Fig. 4. Effects of intravenous administration of vehicle or antagonist (3 mg/0.5 ml/kg) on peak intracerebroventricular ANG II-induced (20 ng/2 μl/kg) pressor responses in normotensive rats. Values are expressed as means ± S.E.M.

ined following intravenous antagonist (3 mg/0.5 ml/kg) or vehicle pretreatment. Fig. 4 displays the results of the pressor tests. Peak pressor responses for the three treatment conditions were 21 ± 6 (vehicle), 16 ± 5 (irbesartan), and 17 ± 2 mmHg (losartan). An ANOVA revealed no significant differences among the three treatment conditions ($P > .05$). Consequently, no follow-up t tests were performed.

3.5. Experiment 5: ANG II-induced blood pressure increases following intracerebroventricular antagonist or vehicle in SHR and WKY

Blood pressure increases were measured in response to intracerebroventricular ANG II (20 ng/2 μl/kg) following intracerebroventricular antagonist (100 μg/2 μl/kg) or vehicle pretreatment. MAP was measured prior to drug pretreatment and 30, 60, 150, 300, and 600 s following ANG II administration. Fig. 5 shows the results of the pressor tests.

Mixed-design ANOVAs and t tests (with a Bonferroni correction for multiple comparisons) were performed at individual time points both prior to and following ANG II administration. In SHR, a main effect of time was found [$F(2,75) = 8.78$, $P < .05$]. Neither a main effect of group nor an interaction effect was found ($P > .05$). A priori t tests demonstrated no significant differences among the pretreatments at baseline and at 600 s post-ANG II ($P > .05$ for all comparisons). However, at 30, 60, 150, and 300 s following ANG II administration, the pressor response to irbesartan was significantly lower than the response to losartan. In WKY, main effects of group [$F(2,60) = 5.26$, $P < .05$] and time [$F(4,60) = 2.82$, $P < .05$] were found. No interaction effect was found ($P > .05$). The t tests revealed no significant differences among the three treatments at baseline and at 150, 300, and 600 s post-ANG II. MAP following irbesartan administration was significantly lower than that following vehicle at 30 and 60 s post-ANG II.

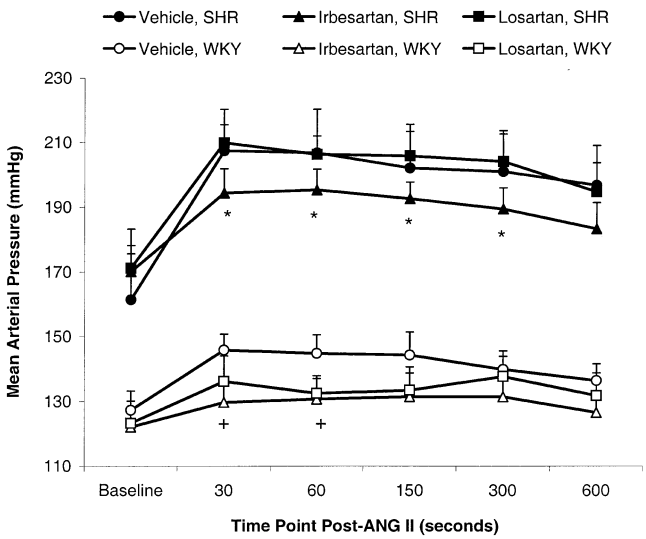

Fig. 5. Effects of intracerebroventricular administration of vehicle or antagonist (100 μg/2 μl/kg) on intracerebroventricular ANG II-induced (20 ng/2 μl/kg) pressor responses in SHR and WKY. Values are expressed as means ± S.E.M. * Irbesartan is significantly different from losartan at $P < .05$. + Irbesartan is significantly different from vehicle at $P < .05$.

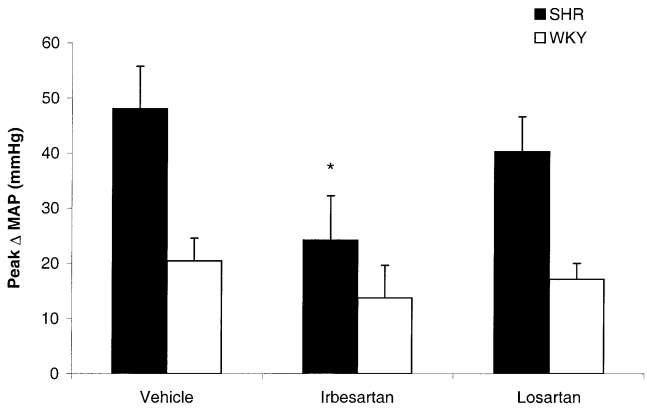

Fig. 6. Effects of intracerebroventricular administration of vehicle or antagonist (100 μg/2 μl/kg) on peak intracerebroventricular ANG II-induced (20 ng/2 μl/kg) pressor responses in SHR and WKY. Values are expressed as means ± S.E.M. * $P < .05$ vs. vehicle in respective group.

The peak pressor response to intracerebroventricular ANG II (20 ng/2 μl/kg), compared to baseline, was examined in SHR and WKY following intracerebroventricular antagonist (100 μg/2 μl/kg) or vehicle pretreatment. Fig. 6 displays the results of the pressor tests. In SHR, the peak increase in MAP (from baseline) following vehicle was 48 ± 8 mmHg. Following irbesartan and losartan, the peak increases in SHR were 24 ± 8 and 40 ± 6 mmHg, respectively. In WKY, the peak increases in MAP were 20 ± 4 (vehicle), 14 ± 6 (irbesartan), and 17 ± 3 mmHg (losartan).

An ANOVA performed on SHR data yielded only marginally significant differences in ANG II-induced blood pressure among the three treatment conditions [$F(2,9) = 2.72$, $P < .1$]. The t tests showed significant differences between vehicle and irbesartan [$t(6) = 2.15$, $P < .05$], marginally significant differences between irbesartan and losartan [$t(6) = 1.57$, $P < .1$], and no significant differences between losartan and vehicle ($P > .05$).

An ANOVA was performed on WKY data, which revealed marginally significant differences in ANG II-induced pressor effects among the three treatment conditions [$F(2,9) = 3.26$, $P < .1$]. The t tests showed marginally significant differences between vehicle and irbesartan [$t(8) = 0.93$, $P < .1$] and no significant differences between either irbesartan and losartan ($P > .05$) or losartan and vehicle ($P > .05$).

4. Discussion

The results of the present studies indicate that there is a complicated relationship between the pharmacological

actions of AT_1 receptor antagonists and the capacity of these agents to affect water consumption and blood pressure. Both irbesartan and losartan exert similar effects on the dipsogenic response to ANG II (intracerebroventricular) at the doses used in the current experiments. However, irbesartan is more effective than losartan at blocking the pressor response to ANG II. The present experiments offer important findings regarding the comparative antihypertensive efficacy of irbesartan and losartan. The examination of both dipsogenic and pressor responses to ANG II allows for a comprehensive analysis of the antihypertensive effects of these drugs. In addition, since the antagonists were administered both centrally and systemically within the same experimental protocol, it is possible to compare directly the effects of the drugs depending upon the route of administration. Finally, the current study allows for conclusions regarding the ability of these agents to affect ANG II-induced pressor responses in both normotensive and hypertensive rats.

The data from Experiments 1 and 2 indicate that irbesartan and losartan act with similar effectiveness to attenuate the dipsogenic response to intracerebroventricular ANG II at the doses presently employed. Both centrally and systemically administered antagonists reduced the dipsogenic response to ANG II in normotensive rats compared to vehicle. These findings, however, do not agree with Culman et al. (1999), who found that irbesartan inhibited intracerebroventricular ANG II-induced drinking more effectively than losartan when the drugs were administered intravenously or orally. While the present results are not wholly consistent with Culman et al., a similar trend was observed. Figs. 1 and 2 indicate that animals treated with irbesartan actually consumed less water than animals treated with losartan (although this difference was not significant).

Central administration of losartan and irbesartan resulted in a greater attenuation of water intake than systemic administration (refer to Figs. 1 and 2). This may be due to the doses employed in the present protocols. However, systemic administration of both antagonists effectively attenuated the drinking response to ANG II, compared to vehicle. These findings are in line with similar research (Culman et al., 1999; Li et al., 1993; Song et al., 1991; Zhuo et al., 1994). Whether the antagonists are crossing the blood–brain barrier or acting within the circumventricular organs (which lack a blood–brain barrier) cannot be directly addressed by the present findings. ANG II interacts with AT_1 receptors in the circumventricular organs (Culman et al., 1999). Therefore, irbesartan and losartan may exert their pharmacological actions without passing through the blood–brain barrier. Conversely, functional studies have demonstrated that both losartan (Song et al., 1991) and irbesartan (Polidori et al., 1998) readily cross the blood–brain barrier. A more specific analysis of the actions of these drugs is needed to determine the site(s) at which these drugs are exerting their antihypertensive effects.

While the data regarding dipsogenic responses in the present experiments can be unambiguously interpreted, the effects of irbesartan and losartan on pressor responses do not offer the same clarity. In contrast to the results from Experiments 1 and 2, the data from Experiment 3 indicate that, at the dose used in the present experiments, irbesartan is more effective than losartan at blocking ANG II-induced pressor responses in normotensive rats. When the antagonists were administered intracerebroventricularly, the peak pressor response to intracerebroventricular ANG II was significantly reduced by irbesartan, compared to both losartan and vehicle. The comparison between losartan and vehicle, on the other hand, produced no significant differences.

In Experiment 4, when the antagonists were administered systemically to normotensive animals, neither irbesartan nor losartan attenuated the pressor response to intracerebroventricular ANG II. The present findings should be interpreted within the context of other similar experiments. The data from Experiment 4 are consistent with Christophe et al. (1995), who found that neither irbesartan (3 mg/kg iv) nor losartan (6 mg/kg iv) reversed the ANG II-induced pressor response in the pithed rat. However, the fact that these experimenters employed systemic administration of ANG II (0.3 μg/kg iv) makes it difficult to draw direct comparisons to the present results. In contrast to the present results are data from Culman et al. (1999), demonstrating that irbesartan and losartan equipotently inhibited pressor responses to both intracerebroventricular and intravenous ANG II.

Experiment 5 examined the pressor responses to centrally administered antagonists and centrally administered ANG II in hypertensive rats and the appropriate control strain. In SHR, intracerebroventricular administration of irbesartan was more effective than losartan at blocking the pressor response to intracerebroventricular ANG II. As displayed in Fig. 5, the administration of irbesartan significantly attenuated blood pressure increases at 30, 60, 150, and 300 s following ANG II administration, compared to losartan. Compared to vehicle, the peak pressor response to ANG II was significantly reduced in animals following irbesartan pretreatment (Fig. 6). Conversely, the difference in peak MAP between losartan and vehicle was not significant. These findings are inconsistent with DePasquale et al. (1992), who found that centrally administered losartan (10 μg icv) blocked the pressor effect of intracerebroventricular ANG II (100 ng). The present study employed a greater dose of losartan and lower dose of ANG II than DePasquale et al., which may not allow for a direct comparison between the two studies. While the ANG II-induced pressor responses were shown to be attenuated by irbesartan in SHR and WKY, the present results do not speak to the effects of the antagonists on baseline blood pressure. However, reductions in basal blood pressure in SHR have been demonstrated following acute and chronic administration of irbesartan and losartan (Lacour et al., 1994; Timmermans et al., 1993; Wong et al., 1990).

Taken together, the current results suggest that irbesartan may be a more effective antihypertensive agent than losartan in both normotensive and hypertensive rats at the doses employed in the present experiments. However, many factors must be considered in the interpretation of the present results. First, although losartan is less lipophilic and possesses a lower affinity for the AT_1 receptor subtype than irbesartan, it is important to recognize that the rapid conversion of losartan to its active metabolite, EXP 3174, enhances its potency. EXP 3174 has approximately a 10–20-fold higher affinity for the AT_1 receptor than losartan (Timmermans et al., 1993), and it has also been shown to cross the blood–brain barrier more effectively than losartan (Polidori et al., 1996). Therefore, it would be useful to perform further research to determine whether EXP 3174 can effectively enhance the antihypertensive properties of losartan.

Second, fluid intake may be a more sensitive measure than blood pressure for elucidating the relative potencies of irbesartan and losartan. It has been suggested that ANG II-induced pressor responses to AT_1 receptor antagonists may be indirectly affected by such factors as baroreceptor activity or baseline blood pressure (Culman et al., 1999). Therefore, with regard to fluid intake, the present experiments demonstrate that irbesartan and losartan display equal effectiveness at the current doses.

A third important consideration for interpreting the present results is that the efficacy of AT_1 receptor antagonists may depend upon the route of administration. The rate of central nervous system penetration of peripherally administered antagonists may depend upon other factors in addition to lipophilicity and affinity for the AT_1 receptor subtype. The data from the present study indicate that both drinking and pressor responses to ANG II are attenuated to a greater extent when irbesartan and losartan are administered centrally rather than systemically. This suggests that penetration into the central nervous system is important for the antagonism of drinking and pressor responses to ANG II. Consistent with this theory are data from Fregly and Rowland (1991), who found that centrally administered losartan potently inhibited the drinking response to intracerebroventricular ANG II but did not affect the drinking response to peripherally administered ANG II. Therefore, the results concerning central administration of irbesartan and losartan, as opposed to systemic administration, may offer a more relevant explanation of the actions of these drugs. However, with regard to the clinical effectiveness of irbesartan and losartan, it will be important to examine specifically the physiologic and pharmacokinetic aspects that may affect the ability of these agents to access the central nervous system following peripheral administration.

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