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Sar[1]-Ala[8] Angiotensin II Blocks Renin-Angiotensin but not Beta-Adrenergic Dipsogenesis[1]

MAISY TANG AND JOHN L. FALK

Department of Psychology, Rutgers University, New Brunswick, New Jersey 08903

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TANG, M. AND J. L. FALK. *Sar[1]-Ala[8] angiotensin II blocks renin-angiotensin but not beta-adrenergic dipsogenesis.* PHARMAC. BIOCHEM. BEHAV. 2(3) 401–408, 1974. – Continuous, intravenous (IV) infusion (10 μg/min) of Sar[1]-Ala[8] angiotensin II (P-113), an angiotensin II blocking analog, into rats greatly attenuated water intake resulting from IV renin (4 U) and IV angiotensin II (80 μg). P-113 infusion did not attenuate the drinking induced by the subcutaneous (SC) administration of beta-adrenergic agents: isoproterenol (0.05 mg/kg), quinterenol (4 mg/kg), and diazoxide (40 mg/kg). P-113 also functioned as a weak agonist with respect to the drinking response. It was concluded that beta-adrenergic dipsogenesis in not attributable to renin release but does depend upon some unknown renal endocrine factor.

Drinking Angiotensin Renin Sar[1]-Ala[8] Angiotensin II Angiotensin blocker Beta-adrenergic Isoproterenol Quinterenol Diazoxide Water-electrolyte balance

TEN YEARS ago, J. O. Davis indicated that: "The discovery of chemicals which block the renin-angiotensin system should provide useful experimental tools. More important to the physician, however, is the possibility of discovering blocking agents which will be useful in the treatment of disease secondary to increased activity of the renin-angiotensin system" [8]. Subsequently, angiotensin-converting enzyme inhibitors [6, 9, 26, 40], as well as angiotensin II analogs functioning as blockers [34, 41, 42, 44, 45, 48] have become available. While presently of too short a duration of action to be useful clinically, these agents have proven valuable in analyzing the role of the renin-angiotensin system in the genesis and maintenance of various forms of hypertension [3, 5, 10, 25, 29, 30, 38, 39, 42]. Lately, these same tools have been applied to analyzing the contribution of the renin-angiotensin system to fluid intake resulting from various stimuli [4, 7, 13, 32, 46, 49].

One question which has not yet been resolved is whether the marked drinking observed in water-satiated animals administered beta-adrenergic drugs [14, 19, 22, 27, 28, 33, 43] is a consequence of increased plasma renin activity (PRA). The increased PRA values, which result from the peripheral administration of beta agonists [1,24] yield an increase in plasma angiotensin II. The peripheral [22] or central [12] administration of angiotensin II itself, even in the physiological dose range [11], produces water intake in the rat. Therefore, according to some [27, 35, 36, 37, 38], but not all [15, 31, 32] investigators, the mechanism of action underlying beta-adrenergically-induced drinking is the generation of angiotensin II which then stimulates certain brain loci producing drinking. Fortunately, the recent availability of angiotensin II blocking analogs made it feasible to test this notion rather directly by administering various beta-adrenergic, dipsogenic agents subcutaneously to rats when they were being infused intravenously with either a saline control or the blocking agent Sar[1]-Ala[8] angiotensin II. Blockade of dipsogenically active intravenous doses of renin and angiotensin II by Sar[1]-Ala[8] angiotensin II was established to validate that the blocker antagonized drinking attributable to the renin-angiotensin system. Subcutaneous doses of three different beta agonist dipsogens were administered at levels which produced drinking approximately equivalent to that evoked by the renin and angiotensin doses utilized.

METHOD

Animals. Twenty male, albino rats (Holtzman strain) with a mean body weight of 372 g (range: 347–415 g) were used. They were housed individually during the experiment in a temperature-controlled room under continuous illumination.

Jugular cannula. Animals were anesthetized with sodium pentobarbital (45 mg/kg) administered intraperitoneally

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(IP). Upon anesthetic induction, atropine sulphate (2 mg, IP) was injected to minimize respiratory congestion. If necessary, animals were supplemented with chloral hydrate (45 mg, IP) to insure anesthesia throughout the operation. Cannula construction and implantation were slightly modified from a previously described procedure [47]. A 2-section cannula consisting of PE 50 and Silichem tubing (Type A, O.D. = 0.031 in, New Brunswick Surgical) was used, with the PE section exiting through a scalp incision into a feedthrough-swivel assembly (BRS/LVE). This assembly was mounted in a Plexiglas ceiling fashioned to fit a standard stainless steel, single rat cage (Acme Research Products) permitting intravenous (IV) infusion into unrestrained animals with a Razel syringe pump (Model A-99).

Drugs. Sar^1-Ala^8 angiotensin II in the acetate form (referred to as P-113) was generously supplied by Dr. Alan W. Castellion, Norwich Pharmacal Co. It was administered IV at 10 μg/min/rat in a solution of 400 μg/ml. Hog renin was purchased from Nutritional Biochemicals Corp. and was given IV at 2 U/min/rat in a solution containing 80 U/ml. Total renin dose per treatment was always 4 U/rat. Asn^1-Val^5-angiotensin II (angiotensin II) was generously supplied by Dr. A. J. Plummer of Ciba Pharmaceutical Co., Summit, New Jersey, as Hypertensin (83% Asn^1-Val^5-angiotensin II, 17% ammonium acetate) and was administered IV at 22.8 μg/min/rat in a solution containing 1 mg/ml. Total angiotensin II dose per treatment was always 80 μg/rat. Infusion rate was constant at 0.025 ml/min for all IV drugs including saline controls. All the above drugs were dissolved in sterile saline and sterile technique was followed for both the preparation and administration of these agents.

Diazoxide (3-methyl-7-chloro-1,2,4-benzothiadiazine-1, 1-dioxide) was obtained as a gift from Dr. Arax Gulbenkian, Schering Corp. It was dissolved in a solution containing 1 part 1 N NaOH to 3 parts 0.9% NaCl. Diazoxide dose per treatment was always 40 mg/kg (SC). Isoproterenol hydrochloride was purchased from Winthrop Laboratories and always given at a dose of 0.05 mg/kg (SC) dissolved in saline. Quinterenol, 1-[5-(8-hydroxyquinolyl)]-2-isopropylaminoethanol, was obtained from Pfizer, Inc., through the courtesy of Dr. P. F. Moore. It was always given at a dose of 4 mg/kg (SC) dissolved in saline. All drug doses, except renin, are specified as the weight of the salt.

Food and water availability. At least 20 hr elapsed from the completion of jugular cannulation to the initial drug infusion. Food (Purina Laboratory chow, pelleted) and water were available continuously except that food was removed during drug infusion sessions. On drug infusion days, 30 min prior to the initial infusion animals were weighed, food was removed and the water supply (Richter tube) was refilled.

EXPERIMENT 1: SAR^1-ALA^8 ANGIOTENSIN II BLOCKADE OF RENIN-INDUCED DRINKING AND LACK OF EFFECT ON DIAZOXIDE-INDUCED DRINKING

In the first set of experiments, the effect of the angiotensin II blocking agent on renin-induced drinking was determined. Intravenously administered renin has been shown to produce drinking in rats [21]. It was important to ascertain whether the blocking analog would prevent renin-induced drinking in light of the recent evidence that angiotensin I is active dipsogenically independent of its conversion to angiotensin II [4,46]. Blocking of renin-induced drinking by the analog would preclude any question that only angiotensin II-induced drinking was being blocked and not that possibly evoked by angiotensin I prior to its conversion.

This experiment also investigated whether the drinking induced by diazoxide [16], which has been shown to depend upon its beta-adrenergic action [18], could be blocked by the angiotensin II analog.

Procedure for Group 1. The administration of a dipsogenic agent (renin or diazoxide) was preceded by either a 20 min infusion of the angiotensin II blocking analog (P-113) or a 20 min blocker control saline infusion (0.9% NaCl). This was followed by continued infusion of the substance given prior to the dipsogenic agent (either P-113 or saline) for 30 min (in the case of renin infusion) or 60 min (in the case of diazoxide injection). These sequences are summarized in diagramatic form in Fig. 1, Panel A. Water intake was recorded at 20 min after the initiation of infusion and after a total of 50 min in the case of renin, and 80 min in the case of diazoxide.

On the day after surgery, six animals were started on the initial infusion. Saline was infused for 20 min, renin for 2 min (2 U/min/rat), and saline again for 30 min. Two and one-half hr later, a similar infusion sequence was employed except P-113 was infused (10 μg/min/rat) in place of saline. Again, 2.5 hr following the termination of the second infusion sequence, a third infusion sequence identical to the first sequence was given. On the following day, the fourth infusion sequence was administered. This consisted of the same 20 min P-113 infusion followed by 40 mg/kg diazoxide (SC) and continued P-113 infusion for another 60 min. On the fifth day after the fourth infusion sequence, P-113 was infused for a total of 80 min.

Procedure for Group 2. A second group of 6 cannulated animals was given 3 infusion sequences. First, a 20 min P-113 infusion preceded a 4 U renin infusion and P-113 was continued for another 30 min. After a 2.5 hr interval a second infusion sequence was given consisting of a 20 min blocker control saline infusion preceding a 4 U renin infusion, with saline infusion continuing for another 30 min. One day later, the third infusion sequence was administered consisting of a 20 min blocker control saline infusion followed by a 40 mg/kg (SC) diazoxide injection with saline infusion continuing for another 60 min after the diazoxide injection.

Results

The results in Experiment 1 are summarized in Fig. 2 (Group 1) and Fig. 3 (Group 2). Inspection of the first 3 infusion sequences in Fig. 2 shows that P-113 infusion greatly attenuated the dipsogenic effect of renin. Thus, in one day, P-113 significantly depressed (t = 3.90, df = 5, $p<0.02$) renin-induced drinking compared to the first infusion sequence (saline-renin) and renin dipsogenesis returned to a high level as shown by the response to the third infusion sequence. In fact, the intake response to this third renin dose was significantly greater (t = 4.063, df = 5, $p<0.01$) than to the first dose. The attenuation produced by P-113 was not a function of the drug treatment order, for when P-113 blockade was the first infusion sequence rather than the second, the same phenomenon occurred (see Fig. 3, infusion sequences 1 and 2).

Comparing the drinking induced by diazoxide under P-113 blockade and saline control conditions (see Fig. 2, infusion sequence 4 and Fig. 3, infusion sequence 3), it is evident that P-113 did not attenuate this response.

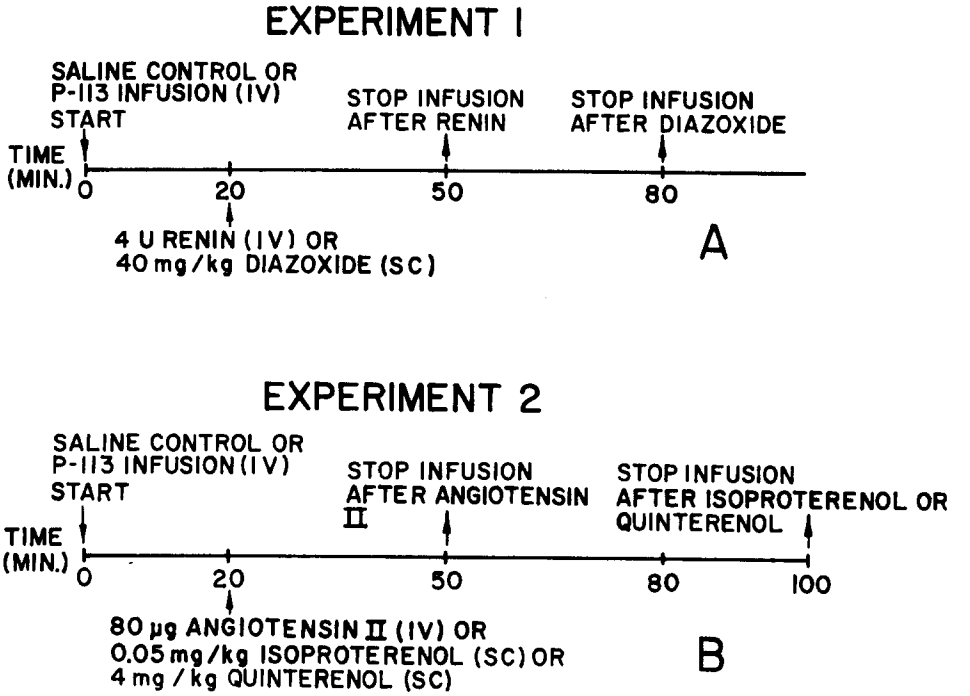

FIG. 1. Infusion sequences used in Experiment 1 (Panel A) and Experiment 2 (Panel B). Water intake determined after the first 20 min infusion of saline control (0.025 ml/min) or P-113 (Sar^1-Ala^8 angiotensin II, 10 µg/min) and again after some fixed time following the administration of a dipsogenic drug at 20 min. Infusion of the saline or P-113 continued throughout the entire drinking period.

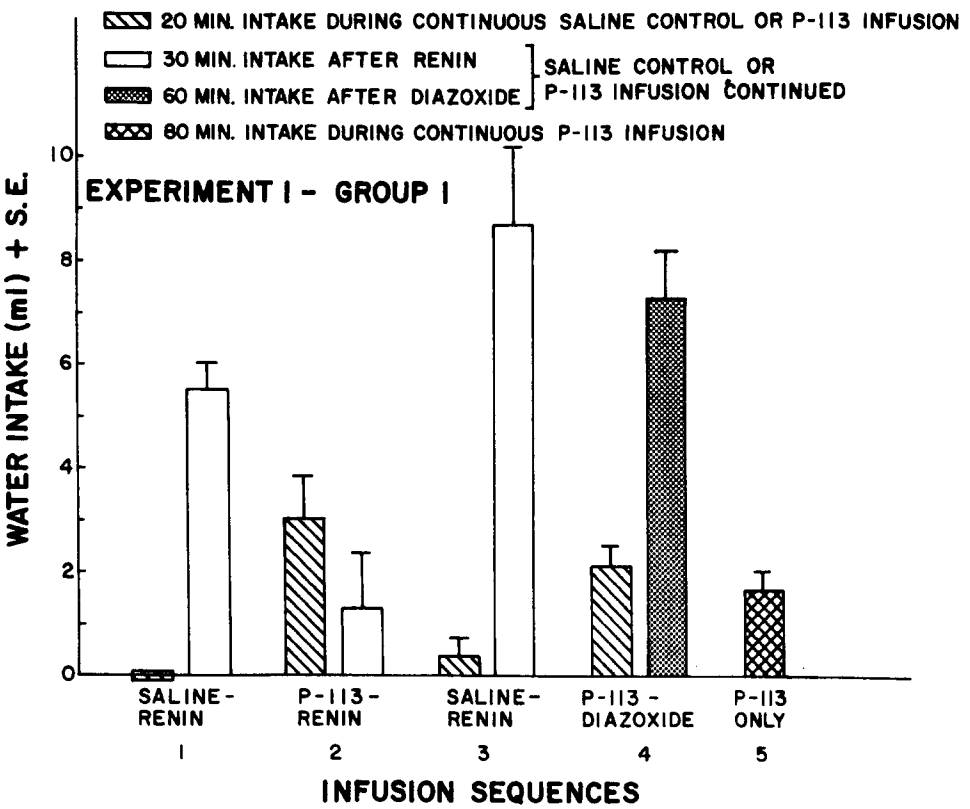

FIG. 2. Water intake of satiated rats determined after 20-min infusion of either saline control or 10 µg/min of angiotensin blocker P-113 (first bar of each set) and again after a dipsogenic stimulus (4 U renin, IV or 40 mg/kg diazoxide, SC) and continued infusion of saline or blocker for 30 min (in the case of renin) and 60 min (in the case of diazoxide). All rats (N = 6) given all infusion sequences in the

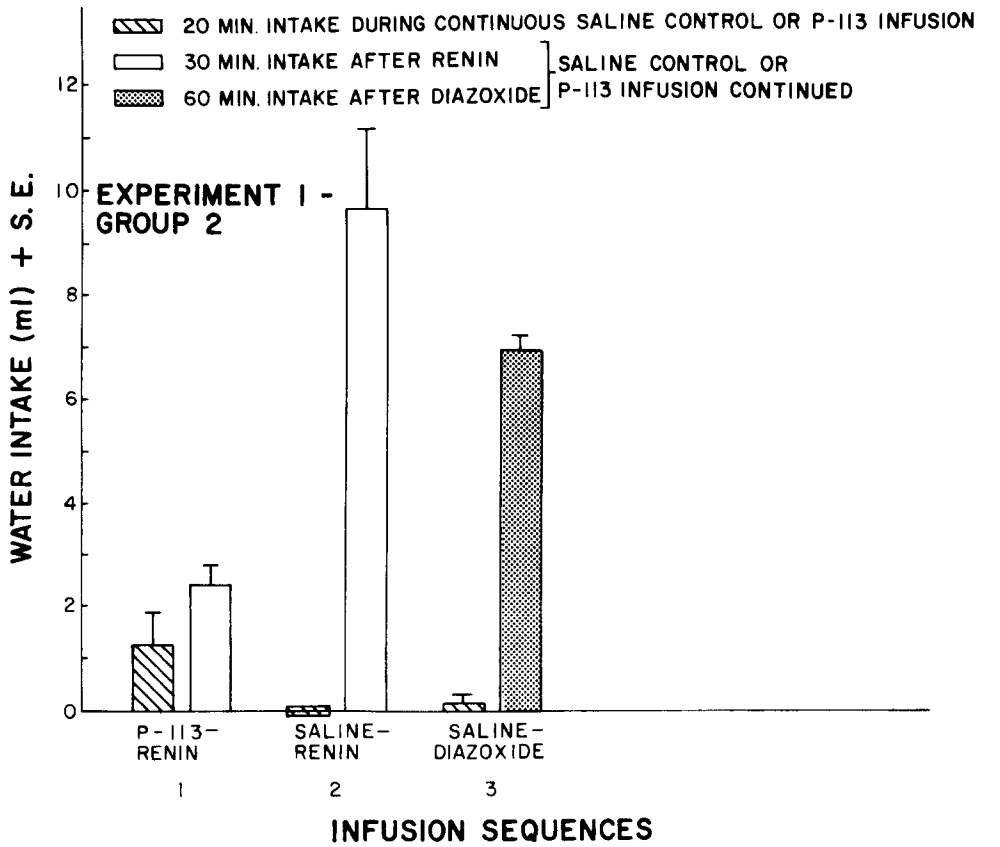

FIG. 3. Water intake of satiated rats determined after 20-min infusion of either saline control or 10 μg/min of angiotensin blocker P-113 (first bar of each set) and again after a dipsogenic stimulus (4 U renin, IV or 40 mg/kg diazoxide, SC) and continued infusion of saline or blocker for 30 min (in the case of renin) and 60 min (in the case of diazoxide). All rats (N = 6) given all infusion sequences in the 1–3 order.

In all cases (Figs. 2 and 3), when P-113 was infused either alone for 80 min or for the 20 min preceding renin or diazoxide, moderate but appreciable drinking occurred. For the 20 min periods, the P-113-induced drinking was always greater than that occurring during comparable 20 min saline infusions. This point is investigated further in Experiment 2.

EXPERIMENT 2: SAR[1]-ALA[8] ANGIOTENSIN II BLOCKADE OF ANGIOTENSIN II-INDUCED DRINKING AND LACK OF EFFECT ON QUINTERENOL- AND ISOPROTERENOL-INDUCED DRINKING

In this experiment, it was determined if the blocking agent (P-113) would occlude the dipsogenic effect of angiotensin II. Also, since isoproterenol and quinterenol are beta-adrenergic agents which produce drinking [17,33], they were administered under P-113 and control saline infusion conditions to ascertain if they, like diazoxide, remained dipsogenically unattenuated by the angiotensin II blocking agent.

Procedure for Group 3. Four rats were cannulated and the general procedures for infusion and water intake measurement were as described above for previous groups. For the first infusion sequence, 20 min of P-113 infusion preceded a quinterenol dose of 4 mg/kg (SC) and P-113 infusion continued for an additional 80 min. See Fig. 1, Panel B, for a diagram of this as well as the other infusion sequences for Experiment 2. Two days later, saline alone was infused for 100 min. Following a 2.5 hr delay, P-113 alone was infused for 100 min. On the next day, 20 min of P-113 infusion preceded an isoproterenol dose of 0.05 mg/kg (SC) and P-113 infusion continued for an additional 80 min.

Procedure for Group 4. Four rats were cannulated and the general procedures were as described above. For the first infusion sequence, 20 min of saline infusion preceded an angiotensin II infusion of 80 μg and saline infusion continued for an additional 30 min. Two and one-half hr later, 20 min of P-113 infusion preceded an angiotensin II infusion of 80 μg and P-113 infusion continued for an additional 30 min. After a 2.5 hr delay, a third infusion sequence identical to the first (saline-angiotensin II) was administered. On the next day, 20 min of saline infusion preceded a quinterenol dose of 4 mg/kg (SC) and saline infusion continued for an additional 80 min. Two days later, 20 min of saline infusion preceded an isoproterenol dose of 0.05 mg/kg (SC) and saline infusion continued for an additional 80 min.

Water intakes for both Groups 3 and 4 were recorded at the end of the initial 20 min infusion and at the end of the longer infusion periods which followed injection of a partic-

ular dipsogenic agent. These second periods were 30 min in the case of angiotensin II and 80 min in the case of isoproterenol or quinterenol. On some occasions, only saline or P-113 was infused for 100 min and the water intake was recorded.

Results

As was the case for renin in Experiment 1, angiotensin II-induced drinking was greatly attenuated by P-113 infusion (Fig. 5 infusion sequences 1, 2 and 3). Thus, in one day, P-113 significantly depressed (t = 6.67, df = 3, $p<0.01$) angiotensin-induced drinking compared to the first infusion sequence (saline-angio. II) and angiotensin II dipsogenesis returned to a high level as shown by the response to the third infusion sequence.

The dipsogenic responses to quinterenol and isoproterenol (Fig. 5, infusion sequences 4 and 5) were not blocked by P-113 infusion (compare with Fig. 4, infusion sequences 1 and 4). As was noted in Experiment 1, P-113 infusion itself (see Fig. 4, infusion sequences 2 versus 3) induced a modest dipsogenic effect (t =.5.686, df = 3, $p<0.02$).

DISCUSSION

These experiments demonstrate that the dipsogenic effects of exogeneously administered (IV) renin and angiotensin II are blocked by the Sar^1-Ala^8 angiotensin II analog. This establishes, by implication, that any dipsogenesis attributable to the activation of the renin-angiotensin system should be blocked by this analog. The correlation between the renin release produced by beta agonists and their dipsogenic effects has been interpreted as a mechanism of action [27, 28, 35, 36, 37]. That is, the increased angiotensin II level resulting from an increased PRA has been assumed to account for the increased water intake. This was given indirect confirmation by two additional pieces of evidence. Nephrectomy, which removes the source of renal renin, also blocks the dipsogenic effect of beta-adrenergic agents [27, 28, 36], but not osmotically-induced drinking [20,28]. Further, propranolol inhibits renin release [1, 2, 24] and also antagonizes the dipsogenic effect of beta-adrenergic agonists. However, the present experiments reveal that the angiotensin II blocking agent failed to attenuate beta-adrenergically-induced drinking when infused at a dose rate which almost completely eliminated drinking responses of equal magnitude induced by either renin or angiotensin. The conclusion seems inescapable that although these beta-adrenergic agents are powerful renin releasers and dipsogens and nephrectomy eliminates both these effects, nevertheless some other beta-adrenergically-stimulated renal endocrine factor, unopposed by Sar^1-Ala^8 angiotensin II, determines the dipsogenic response. Indeed, it is curious that beta-adrenergically-induced drinking was not somewhat reduced by P-113 since PRA values were undoubtedly increased by the beta agonists [1,24] and should have contributed at least a minor component to the dipsogenic response. But beta-adrenergically-induced drinking was comparable whether P-113 or the saline con-

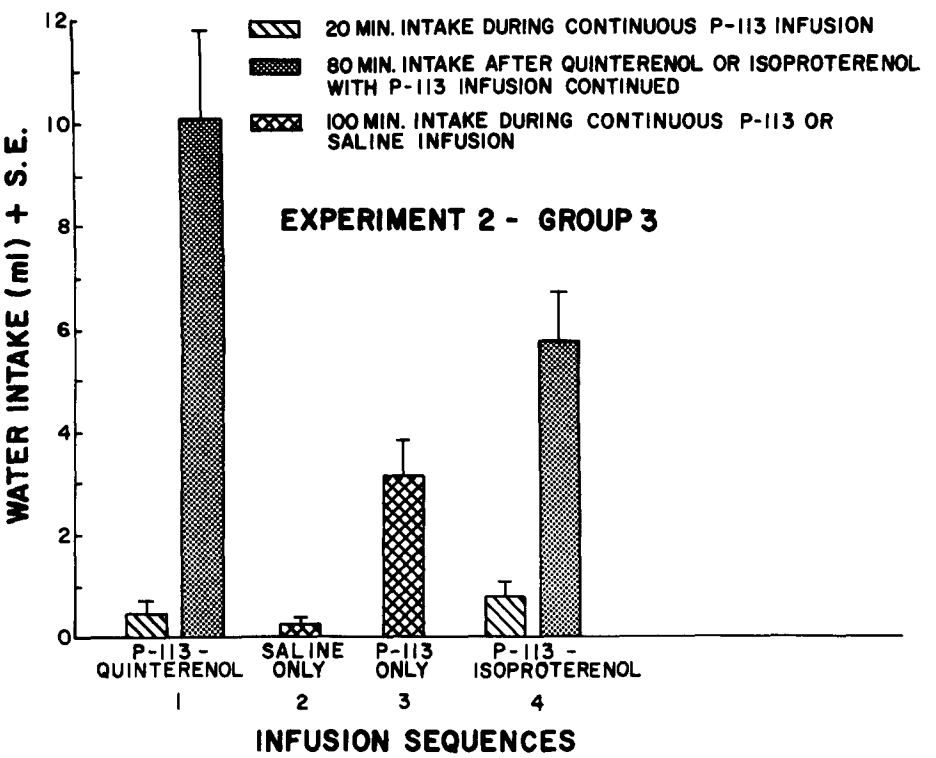

FIG. 4. Water intake of satiated rats determined after 20-min infusion of 10 μg/min of angiotensin blocker P-113 (first bar of infusion sequences 1 and 4) and again 80 min after a dipsogenic stimulus (4 mg/kg quinterenol or 0.05 mg/kg isoproterenol, SC) and continued infusion of blocker. Water intake following 100-min infusions of saline and P-113 determined in infusion sequences 2 and 3. All rats (N = 4) given all infusion sequences in the 1–4 order.

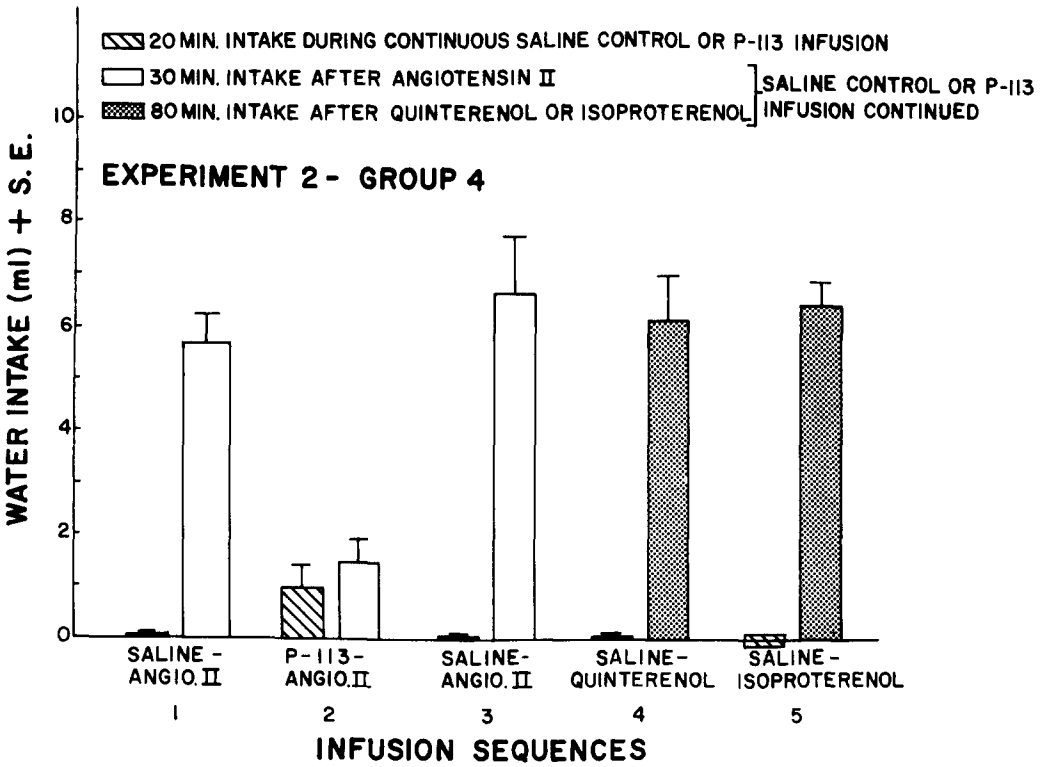

FIG. 5. Water intake of satiated rats determined after 20-min infusion of either saline control or 10 μg/min of angiotensin blocker P-113 (first bar of each set) and again after a dipsogenic stimulus [80 μg angiotensin II (IV), 4 mg/kg quinterenol, or 0.05 mg/kg isoproterenol (SC)] and continued infusion of saline or blocker for 30 min (in the case of angiotensin II) and 80 min (in the case of quinterenol or isoproterenol). All rats (N = 4) given all infusion sequences in the 1–5 order.

trol was infused. It could be argued that the possible beta-stimulated, angiotensin-determined drinking component was obscured by the weak agonist, dipsogenic action of P-113 adding to the drinking graphed as the second bar in each infusion situation involving P-113. However, this weak agonist effect of P-113 was small and variable, with most of the effect occurring during the first 20-min infusion component. By the most liberal interpretation, this effect could not have contributed more than 1–2 ml to the drinking graphed as the second bar in the P-113 infusion sequences.

The weak agonist effect of Sar^1-Ala^8 angiotensin II with respect to the drinking response in rats confirms a similar observation made in cats [7] in which infusion into the lateral ventricles evoked a small dipsogenic effect but also blocked angiotensin II-induced dipsogenesis. Other angiotensin II blocker analogs were found to possess some degree of agonism with respect to the drinking response when placed directly into the brain, although they failed to block angiotensin II-induced drinking when applied to the cerebral site 1 min prior to angiotensin II application [46]. However, in conformity with the present experiments, P-113 applied to the brain or intravenously blocked Ile^5 angiotensin-induced drinking evoked by the same routes [13].

The conclusion reached on the basis of the present studies, that beta-adrenergically-induced drinking is not attributable to renin release and angiotensin II generation, confirmed the import of a related experiment that certain non-beta-adrenergic, renin-releasing agents (hydralazine, sodium nitroprusside) failed as dipsogens [15]. While exogenous renin, angiotensin I, and II can evoke drinking, as do certain agents stimulating the renin-angiotensin system, it apparently does not follow that the dipsogenic efficacy of the renin-releasers is attributable to this release, nor do renin-releasers necessarily insure dipsogensis.

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