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Effect of the Presynaptic Dopaminergic Agonist, Quinpirole, on the Drinking Responses of Rats to Angiotensin II, Isoproterenol, and Hypertonic Saline[1]

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FREGLY, M J AND N E ROWLAND *Effect of the presynaptic dopaminergic agonist, quinpirole, on the drinking responses of rats to angiotensin II, isoproterenol, and hypertonic saline* PHARMACOL BIOCHEM BEHAV **24**(3) 721–725, 1986 —The dopamine (DA_2) agonist, quinpirole hydrochloride (LY 171555), has been reported to inhibit central presynaptic release of norepinephrine, an effect similar to that of clonidine, an α_2-adrenoceptor agonist Since clonidine exerts an antidipsogenic effect on all types of laboratory-induced drinking, the objective of these experiments was to determine whether administration of quinpirole hydrochloride produced a similar effect The drinking responses of rats to administration of angiotensin II (200 μg/kg, SC), isoproterenol (25 μg/kg, SC), and hypertonic saline (1 M NaCl, 1% of body weight, IP) were blocked by administration of quinpirole hydrochloride (7 5 mg/kg, IP) When administered alone, quinpirole had no effect on water intake Thus, the antidipsogenic effect of quinpirole hydrochloride resembles that of clonidine and suggests that release of norepinephrine occurs centrally at some point along the final common pathway for drinking in rats

Quinpirole hydrochloride LY 171555 Presynaptic dopamine agonist Thirst Angiotensin II Isoproterenol Hypertonic saline

STUDIES from this laboratory have shown that acute administration of an α_2-adrenoceptor agonist, clonidine, to rats can inhibit all forms of laboratory-induced drinking thus far tested including that induced by isoproterenol, angiotensin II (AII), hypertonic saline, serotonin, 5-hydroxytryptophan, and dehydration [4, 5, 7, 9, 17, 20] Others have also shown that clonidine can inhibit dehydration-induced drinking [12] Clonidine is believed to act centrally in the final common pathway for drinking where it inhibits presynaptic release of norepinephrine [20] Thus, it seems likely that all laboratory-induced drinking responses of rats are mediated eventually by norepinephrine

Recently a DA_2-dopamine agonist, quinpirole hydrochloride (LY 171555, trans-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-2H-pyrazolo [3,4-g] quinoline monohydrochloride), has become available This compound has been reported to inhibit presynaptic release of norepinephrine [8,19] It seemed important to test its effect on several types of laboratory-induced drinking to determine whether it could also inhibit the drinking responses to a variety of dipsogenic stimuli

METHOD

Five separate experiments were carried out Each experiment used female rats of the Blue Spruce Farms (Sprague-Dawley) strain All animals were kept in a thermoregulated (26±1°C) room illuminated from 7 a m to 7 p m Purina Laboratory Chow and tap water were provided ad lib All drinking studies were performed in a quiet room beginning at 9 30 a m Fluid containers consisted of infant nursing bottles with cast aluminum spouts [11] The temperature of the water presented to all rats was 26°C

The data from all experiments were analyzed by a one-way analysis of variance [3] Comparison between individual means was made using the pooled variance from the analysis of variance

Experiment 1 Effect of Graded Doses of Quinpirole Hydrochloride on the Drinking Response to Angiotensin II

Thirty naive rats (250–320 g) were separated randomly into 5 equal groups All groups received AII (200 μg/kg, SC) In addition, the five groups received quinpirole at 0, 0 5, 2 0, 5 0, and 7 5 mg/kg, IP, respectively, immediately prior to treatment with AII After administration of the drugs, each rat was placed in an individual stainless steel metabolic cage and given a preweighed bottle containing distilled water. No food was available to the rats during the study Water intake was measured thereafter at 0 5, 1 0, and 2 0 hr

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TABLE 1

EFFECT OF GRADED DOSES OF QUINPIROLE HYDROCHLORIDE ON THE DRINKING RESPONSE OF FEMALE RATS TO ADMINISTRATION OF ANGIOTENSIN II

Dose of Quinpirole (mg/kg, IP)	N	Body Wt (g)	Cumulative water intake (ml/kg) 0 5	1 0	2 0 hr
0	6	287 ±4	12 2 ±3 7	30 1 ±6 5	35 9 ±7 6
0 5	6	277 ±7	2 1 ±2 1	4 8 ±2 6	6 2 ±2 4
2 0	6	291 ±8	0 8 ±0 4	4 9 ±0 9	8 4 ±1 4
5 0	6	294 ±8	0 9 ±0 5	5 1 ±1 7	7 6 ±3 3
7 5	6	288 ±8	0 0 ±0 0	1 0 ±0 7	2 5 ±1 5
ANOVA		F(4,24)	6 71*	12 48*	11 16*

Mean ± SE are shown All rats received AII (200 μg/kg, SC)
All quinpirole intakes are significantly ($p<0$ 05) less than vehicle-treated rats
*Significant effect of treatment

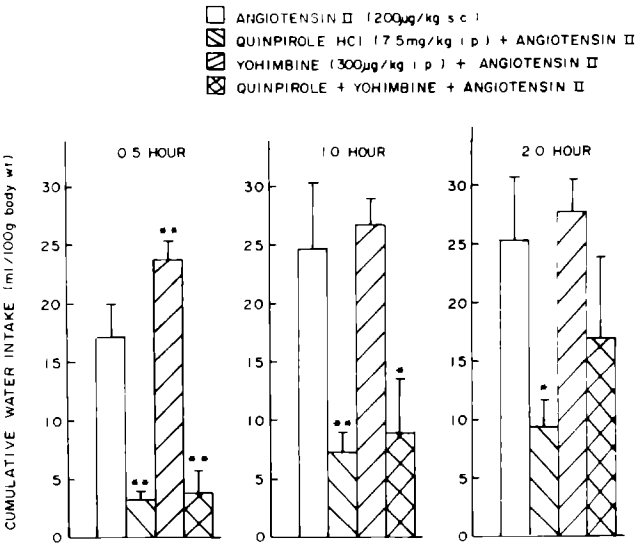

FIG 1 Effect of the α_2-adrenoceptor antagonist, yohimbine, on the antidipsogenic effect of quinpirole on angiotensin II-induced water intake in rats One standard error is set off at each mean $^*p<0$ 05, $^{**}p<0$ 01 compared with the angiotensin II-treated group Groups and doses are designated in the figure

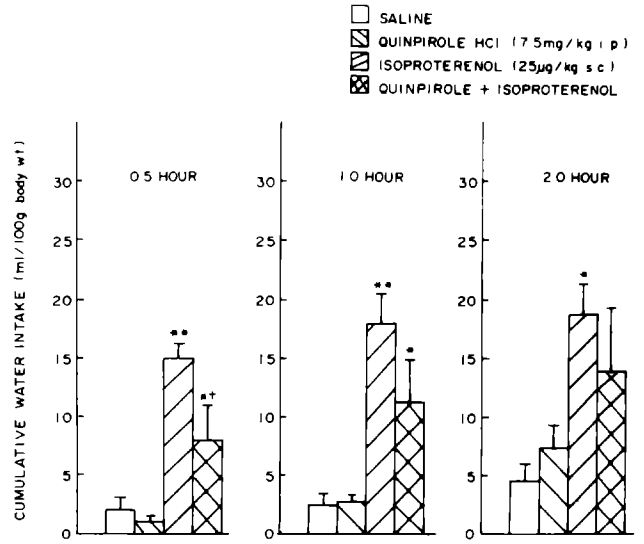

FIG 2 Effect of quinpirole on the drink induced in rats by isoproterenol One standard error is set off at each mean $^*p<0$ 05 $^{**}p<0$ 01 compared with saline-treated control group $^+p<0$ 05 compared with isoproterenol-treated group Groups and doses are designated in the figure

Experiment 2 Effect of Yohimbine on the Antidipsogenic Effect of Quinpirole Hydrochloride in Angiotensin II-Treated Rats

Twenty-four naive rats (250–275 g) were separated randomly into 4 equal groups Group 1 served as a control group, group 2 received quinpirole hydrochloride (7 5 mg/kg, IP) and AII at the same time, group 3 received yohimbine (300 μg/kg, IP) [7], the α_2-adrenoceptor antagonist and AII, while group 4 received quinpirole, yohimbine and AII The remainder of the experiment was identical to that described in Experiment I

Experiment 3 Effect of Peripheral and Central Dopamine Receptor Antagonists on the Antidipsogenic Action of Quinpirole Hydrochloride

This experiment was performed as two separate studies These two studies used female Sprague-Dawley rats (234–308 g) from Zivic Miller Laboratories, Allison Park, PA An additional difference from the studies described above was that water intakes were recorded volumetrically from burettes graduated at 0 1 ml Other details were similar to those described in Experiment 1

The first study examined whether the peripherally acting dopamine antagonist, domperidone, would affect the antidipsogenic response to quinpirole in AII-treated rats Twenty-four rats were separated into four groups, all of which received three injections Food and water were removed prior to the first injection, and water was made available after the last injection which was AII (200 μg/kg, SC) for all rats Group 1 served as control and received two injections (SC then IP) of isotonic saline spaced 30 min apart, the AII injection was given immediately after the second (IP) injection Group 2 received the vehicle SC, then quinpirole hydrochloride (7 5 mg/kg, IP) and AII Group 3 received domperidone (10 0 mg/kg, SC, Janssen Pharmaceutica), then saline and AII Group 4 received domperidone (10 0 mg/kg, SC), then quinpirole hydrochloride (7 5 mg/kg, IP) and AII Water intakes were measured at 0 5, 1 0 and 2 0 hr later

The second study examined whether spiperone, a dopamine antagonist which crosses the blood-brain barrier

TABLE 2

EFFECT OF PERIPHERAL AND CENTRAL DOPAMINE RECEPTOR ANTAGONISTS ON THE ANTIDIPSOGENIC ACTION OF QUINPIROLE HYDROCHLORIDE IN ANGIOTENSIN II-TREATED RATS¶

Treatments (mg/kg)				Cumulative water intake (ml/kg)		
Drug 1	Drug 2	No of rats	Mean Body Wt (g)	0 5	1 0	2 0 hr
Study 1						
Vehicle + Vehicle		6	251 ±5	11 8 ±3 1	17 9 ±3 2	19 0 ±3 4
Vehicle + Quinpirole (7 5 mg/kg, IP)		6	264 ±3	2 2 ±0 6†	5 1 ±1 4†	6 9 ±2 3†
Domperidone + Vehicle (10 mg/kg, SC)		6	268 ±9	9 5 ±2 5	13 0 ±3 6	15 8 ±3 5
Domperidone + Quinpirole		6	255 ±4	1 4 ±1 1†	2 5 ±1 0†	3 0 ±0 8†
ANOVA (F ratios)		First Drug		0 56	2 22	1 72
		Second Drug		17 39†	21 07†	21 12†
		Interaction		0 13	0 19	0 01
Study 2						
Vehicle + Vehicle		11	272 ±5	16 9 ±1 7	21 7 ±1 9	25 0 ±3 2
Vehicle + Quinpirole (7 5 mg/kg, IP)		6	286 ±8	2 5 ±0 7†	5 7 ±0 9†	6 6 ±1 6†
Spiperone + Vehicle (0 03 mg/kg, SC)		11	269 ±6	10 2 ±2 6*	11 8 ±2 5*	11 9 ±2 6*
Spiperone + Quinpirole		12	275 ±4	10 0 ±2 7‡	14 8 ±3 0‡	18 8 ±3 5‡
ANOVA (F Ratios)		First Drug		0 50	1 12	0 90
		Second Drug		6 51*	3 85	1 36
		Interaction		7 78†	12 69†	14 86†

*=$p<0$ 05, †=$p<0$ 01 relative to vehicle-vehicle controls
‡$p<0$ 01=Spiperone+quinpirole greater than quinpirole alone
¶All rats received angiotensin II (200 μg/kg, SC) immediately after the second injection Drug 2 was administered one-half hour after Drug 1

and itself is potently antidipsogenic [17], would affect the antidipsogenic effect of quinpirole on AII-induced drinking The procedure was identical with Study 1, except that spiperone (0 03 mg/kg, SC, Janssen Pharmaceutica) was used instead of domperidone The experiment was run twice with a larger number of animals being assigned to the treatment groups However, no rat was retested after it received spiperone

Experiment 4 Effect of Quinpirole Hydrochloride on the Drinking Response to Isoproterenol

Twenty-four naive rats (225–245 g) were divided into 4 equal groups Group 1 served as a control group and received isotonic saline (1 0 ml/kg, IP), group 2 received quinpirole hydrochloride (7 5 mg/kg, IP), group 3 received isoproterenol (25 μg/kg, SC), while group 4 received both isoproterenol and quinpirole simultaneously The remainder of this experiment was identical to that described in Experiment 1 excepting that urine was not collected

Experiment 5 Effect of Quinpirole Hydrochloride on the Drinking Response to Hypertonic Saline

Twenty-four naive rats (230–265 g) were divided randomly into 4 equal groups Group 1 served as control and received isotonic saline (1 0 ml/kg, IP), group 2 received quinpirole hydrochloride (7 5 mg/kg, IP), group 3 received 1 M NaCl solution (1% of body weight, IP), while group 4 received both quinpirole and 1 M NaCl solution Quinpirole was administered 15 min prior to administration of 1 M NaCl solution The remainder of this experiment was identical to that described in Experiment 1

RESULTS

Experiment 1

Administration of quinpirole at 0 5 mg/kg in combination with AII reduced water intake significantly below that of the group treated with AII alone (Table 1) Higher doses exerted an even greater effect on AII-induced water intake The

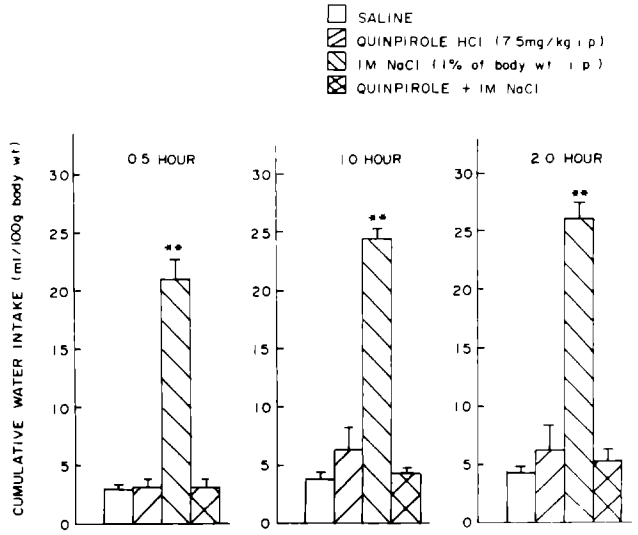

FIG 3 Effect of quinpirole on the drink induced in rats by hypertonic saline One standard error is set off at each mean $^{**}p<0.01$ compared with saline-treated control group Groups and doses are designated in the figure

antidipsogenic effect of all doses of quinpirole continued throughout the 2 hr of the experiment

Experiment 2

Yohimbine, the α_2-adrenoceptor blocker, failed to antagonize the antidipsogenic effect of quinpirole (Fig 1) However, yohimbine enhanced significantly the dipsogenic effect of AII during the first half-hr of the study

Experiment 3

The results of Study 1 are shown in Table 2 As expected, AII induced a large drink which was potently inhibited by quinpirole Baseline water intake of untreated rats was about 4 ml/kg/2 hr (data not shown) Domperidone (drug 1) was without effect on either the AII-induced drinking, or on the antidipsogenic effect of quinpirole (drug 1 and drug 1 × drug 2 interactions were not significant) In other studies (not shown) we found that domperidone (0 1, 1 0 and 10 0 mg/kg) had no effect on either water intake or urine output after administration of either isoproterenol (50 μg/kg, SC) or hypertonic NaCl solution (1 M, SC)

The results of Study 2 are shown in Table 2 AII again induced a large drink which was inhibited by quinpirole There were significant effects of drug 2 (quinpirole) and a drug 1 × drug 2 interaction One way ANOVA and Duncan post-hoc tests showed that spiperone itself suppressed AII-induced drinking (by about 50%) and that it almost completely blocked the antidipsogenic action of quinpirole Specifically, at 1 and 2 hr both spiperone alone and quinpirole alone had significant suppressant effects on AII drinking, but their combination was ineffective

Experiment 4

Isoproterenol-induced water intake was attenuated significantly by quinpirole (Fig 2) The inhibitory effect was not great compared to its effect on AII, however, the effect of lower doses of isoproterenol was not studied

Experiment 5

Hypertonic saline-induced water intake was attenuated significantly by quinpirole (Fig 3) The inhibitory effect was evident at all times during the two hr study

DISCUSSION

Recent studies support the classification of dopamine receptors into DA_1, DA_2, and DA_3 types [13] The DA_2 receptor, at which LY 141865 and its enantiomer, quinpirole, are believed to act is located presynaptically [1 2, 8] in both peripheral and central neurons LY 171555 has been shown to act centrally by virtue of its ability to inhibit the release of prolactin in rats [18], and to induce contralateral rotation in rats having unilateral 6-hydroxydopamine-induced denervation of the striatum [18] Activation of DA_2-receptors in the rabbit hypothalamus has also been shown to inhibit noradrenergic neurotransmission [10,19] In this respect, activation of central DA_2-receptors induces an effect similar to that induced by activation of central presynaptic α_2-adrenoceptors [10] Indeed the effects of clonidine and quinpirole to inhibit various types of laboratory-induced drinking are similar While the antidipsogenic effects of quinpirole on laboratory-induced drinking have not been studied as extensively as clonidine, it is clear that it can inhibit drinking associated with both osmoreceptors (hypertonic saline) and AII receptors (isoproterenol and AII) both of which are located centrally according to our present understanding of them Since this is the case, quinpirole must act at some point in the central nervous system along the final common pathway for drinking, as has been postulated for clonidine [20] It has also been postulated that an essential neurotransmitter in the final common pathway is norepinephrine Inhibition of the release of norepinephrine by activation of either presynaptic α_2-adrenoceptors (by clonidine) or presynaptic DA_2-dopamine receptors (quinpirole) inhibits the response to a variety of dipsogenic stimuli [4, 5, 9, 12, 17 20]

To assure that quinpirole acts centrally, the dopaminergic antagonist, domperidone, which does not cross the blood-brain barrier, was administered in combination with quinpirole and AII Domperidone failed to reverse the antidipsogenic effect of quinpirole In contrast, spiperone, a dopaminergic antagonist that crosses the blood brain barrier reduced the antidipsogenic effect of quinpirole on AII-induced drinking

To assure that quinpirole was not acting at presynaptic α_2-adrenoceptors, the presynaptic α_2-blocker, yohimbine was administered in combination with quinpirole Yohimbine failed to block the antidipsogenic effect of quinpirole but did enhance significantly the drinking response to AII (Fig 1) These results suggest that quinpirole does not produce its antidipsogenic effect by acting at α_2-adrenoceptors

The ability of yohimbine and tolazoline to enhance the drinking responses to isoproterenol and AII has been reported earlier [6] Since these compounds are α_2-adrenoceptor antagonists, it is assumed that they enhance the release of norepinephrine in response to dipsogenic stimuli and therefore enhance the drinking response

The central site at which either quinpirole or clonidine may act to produce their antidipsogenic effects is not known clearly Clonidine is believed to produce its cardiovascular effects in the nucleus tractus solitarius [14 15] Quinpirole may also act in the striatum where it has been reported to

block the dopaminergic inhibition of acetylcholine release [16] Additional studies will be required to clarify the site(s) at which both quinpirole and clonidine act to inhibit laboratory-induced drinking

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