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This study was designed to investigate the role of dopaminergic mechanisms in the control of aldosterone secretion in man. Five normal male subjects in metabolic balance at 150 meq sodium/d and 60 meq potassium/d constant intake received the specific dopamine antagonist, metoclopramide, 10 mg i.v. on 2 consecutive d. On the 1st d, the subjects received an infusion of 5% glucose solution (vehicle) from 60 min before to 60 min after metoclopramide administration; on the 2nd d, an infusion of dopamine 4 µg/kg per min was substituted for vehicle. Metoclopramide in the presence of vehicle increased plasma aldosterone concentrations from 2.4±1.1 to a maximum of 17.2±2.8 ng/100 ml ($P < 0.01$) and serum prolactin concentrations from 7.5±5.0 to a maximum of 82.2±8.7 ng/ml ($P < 0.01$). Dopamine 4 µg/kg per min did not alter basal plasma aldosterone concentrations, but blunted the aldosterone responses to metoclopramide significantly; in the presence of dopamine, plasma aldosterone concentrations increased from 3.1±0.5 to 6.2±1.4 ng/100 ml ($P < 0.05$) in response to metoclopramide. The incremental aldosterone responses to metoclopramide were significantly lower in the presence of dopamine than with vehicle. Dopamine 4 µg/kg per min suppressed basal prolactin to <3 ng/ml and inhibited the prolactin responses to metoclopramide; serum prolactin concentrations increased to a maximum of 8.5±2.3 ng/ml with metoclopramide in the presence of dopamine.

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Dopaminergic Inhibition of Metoclopramide-induced Aldosterone Secretion in Man

DISSOCIATION OF RESPONSES TO DOPAMINE AND BROMOCRIPTINE

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ABSTRACT This study was designed to investigate the role of dopaminergic mechanisms in the control of aldosterone secretion in man. Five normal male subjects in metabolic balance at 150 meq sodium/d and 60 meq potassium/d constant intake received the specific dopamine antagonist, metoclopramide, 10 mg i.v. on 2 consecutive d. On the 1st d, the subjects received an infusion of 5% glucose solution (vehicle) from 60 min before to 60 min after metoclopramide administration; on the 2nd d, an infusion of dopamine 4 $\mu\text{g}/\text{kg}$ per min was substituted for vehicle. Metoclopramide in the presence of vehicle increased plasma aldosterone concentrations from 2.4 ± 1.1 to a maximum of 17.2 ± 2.8 ng/100 ml ($P < 0.01$) and serum prolactin concentrations from 7.5 ± 5.0 to a maximum of 82.2 ± 8.7 ng/ml ($P < 0.01$). Dopamine 4 $\mu\text{g}/\text{kg}$ per min did not alter basal plasma aldosterone concentrations, but blunted the aldosterone responses to metoclopramide significantly; in the presence of dopamine, plasma aldosterone concentrations increased from 3.1 ± 0.5 to 6.2 ± 1.4 ng/100 ml ($P < 0.05$) in response to metoclopramide. The incremental aldosterone responses to metoclopramide were significantly lower in the presence of dopamine than with vehicle. Dopamine 4 $\mu\text{g}/\text{kg}$ per min suppressed basal prolactin to < 3 ng/ml and inhibited the prolactin responses to metoclopramide; serum prolactin concentrations increased to a maximum of 8.5 ± 2.3 ng/ml with metoclopramide in the presence of dopamine.

The subjects were studied in the same manner except that dopamine 2 $\mu\text{g}/\text{kg}$ per min was adminis-

tered instead of the 4- $\mu\text{g}/\text{kg}$ per min dose. Dopamine 2 $\mu\text{g}/\text{kg}$ per min attenuated the aldosterone and prolactin responses to metoclopramide, but was less effective than the 4- $\mu\text{g}/\text{kg}$ per min dose of dopamine.

Metoclopramide 10 mg i.v. was administered to five additional subjects after pretreatment with the dopamine agonist, bromocriptine, 2.5 mg or placebo at 6 p.m., midnight, and 6 a.m. before study. Bromocriptine suppressed basal serum prolactin levels and completely inhibited the prolactin responses to metoclopramide. In contrast, bromocriptine did not alter basal plasma aldosterone concentrations or the aldosterone responses to metoclopramide. Plasma renin activity, plasma cortisol, and serum potassium concentrations were unchanged by metoclopramide, dopamine, or bromocriptine.

The results of this study suggest that the aldosterone response to metoclopramide is mediated by metoclopramide's antagonist activity at the dopamine receptor level. The results further suggest dissociation of the responses to the dopamine agonists, dopamine and bromocriptine, and indicate that a new type of dopamine receptor may inhibit aldosterone secretion.

INTRODUCTION

Metoclopramide [*N*-diethylaminoethyl]-2-methoxy-4-amino-5-chlorobenzamide], a procainamide derivative, is a competitive antagonist of dopamine in the central nervous system (1-4), gut (5), and cardiovascular system (6). Metoclopramide stimulates prolactin secretion from the pituitary gland in vivo in experimental animals and man (7-13), and antagonizes the inhibitory effect of dopamine on prolactin release in vitro (14). Of the dopamine receptor antagonists cur-

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rently available, metoclopramide appears to be the most specific (15).

Recent studies from this laboratory (16) have demonstrated that metoclopramide stimulates aldosterone production in normal man. The increase in aldosterone production could not be attributed to increase in any of the known factors that stimulate aldosterone or to increases in prolactin. On the other hand, bromocriptine (2-brom- α -ergocryptine), a specific dopamine agonist, neither decreased basal aldosterone production nor inhibited angiotensin II-induced aldosterone secretion. Taken together, these observations suggested that, in normal man, aldosterone production may be under maximum "tonic" dopaminergic inhibition, which can be overridden by the renin-angiotensin system (16).

The present study was designed to investigate further the role of dopaminergic mechanisms in the control of aldosterone production in normal man. The rationale for this study may be stated simply. If metoclopramide stimulates aldosterone production by antagonizing dopamine at dopamine receptor sites, then metoclopramide-induced aldosterone production should be inhibited by dopaminergic agonists. Thus, the effects of both dopamine and the dopamine agonist, bromocriptine, on metoclopramide-induced increases in plasma aldosterone concentration were determined. During these experiments, potassium, ACTH (as reflected by plasma cortisol concentrations), and the renin-angiotensin system, which are all known to influence aldosterone, and prolactin, an index of dopamine receptor effects, were also studied.

METHODS

10 normal white male volunteer subjects, 20–30 yr, with normal arterial blood pressure and no history of renal disease were studied. The protocol was approved by the Human Experimentation Committee of the University of Virginia Medical Center and written informed consent was obtained from all subjects. Before study, the subjects were placed on a constant diet containing 150 meq of sodium, 60 meq of potassium, 1 g of protein/kg, and 2,680 cal/d for 5 d at the Clinical Research Center. Consecutive 24-h urine samples were collected for the first 4 d of the diet, and consecutive 12-h urine samples were collected for the remainder of each study and were analyzed for sodium, potassium, and creatinine.

Metoclopramide/dopamine studies. Five of the subjects were studied in the following manner. No food was given after midnight before study day 1, when the subjects assumed the supine position until completion of the study. At 6:00 a.m. of study day one, a heparin lock for obtaining blood samples was placed in the left antecubital vein and an intravenous infusion of 5% glucose solution (D_5W)¹ at 1 ml/min was begun in the right antecubital vein. At 6:30 a.m., the subjects completed their 12-h urine collections and blood pressure

monitoring with an Arteriosonde (Hoffman-LaRoche, Inc., Nutley, N. J.) was initiated and continued every 2 min until completion of study. At 7:00 a.m., control blood samples were obtained for determination of serum sodium, potassium, and prolactin concentrations, and plasma renin activity, cortisol, and aldosterone concentrations. After completion of blood sampling at 7:00 a.m., an intravenous infusion of D_5W (vehicle) at 0.1 ml/min was initiated with a Harvard infusion pump (Harvard Apparatus Co., Inc., S. Natick, Mass.) and was continued for 120 min (–60–60 min of the study). Blood sampling was repeated at 7:30 and 8:00 a.m. (–30 and 0 min of the study). After completion of the blood sampling at 8:00 a.m., an intravenous bolus dose of metoclopramide (10 mg) was given. Blood samples were then obtained at 10, 20, 30, and 60 min (8:10, 8:20, 8:30, and 9:00 a.m.) after metoclopramide injection. At 9:00 a.m., the D_5W (vehicle) infusion was discontinued and further blood sampling accomplished at 9:30 and 10:00 a.m. (90 and 120 min after metoclopramide administration).

After completion of the study at 10:00 a.m., the subjects continued on the constant diet and urine collections. On study day 2, an identical protocol as for study day one was carried out except that, instead of D_5W vehicle, dopamine hydrochloride 2 μ g/kg per min was infused for 120 min beginning at 7:00 a.m. The diet was discontinued and the subjects were discharged from the Clinical Research Center after completion of the final urine collection at 6:30 p.m. on study day 2. The total volume of blood obtained from each subject during the 2nd study was 500 ml.

After a 4–6 wk interval on an ad lib. diet, the same subjects were placed again on the same constant diet at the Clinical Research Center for 5 d before study. Urine collections were obtained as before. The subjects then underwent an identical protocol on study days 1 and 2 as described above for the metoclopramide/dopamine studies except that 4 μ g/kg per min of dopamine was substituted for the 2 μ g/kg per min quantity of dopamine administered on study day 2.

Metoclopramide/bromocriptine studies. The remaining five subjects were studied with an identical protocol as for the metoclopramide/dopamine studies with the following exceptions. Dopamine or vehicle were not administered. Instead, the subjects received placebo capsules orally at 6:00 p.m. and midnight before study day 1 and at 6:00 a.m. on study day 1. At 7:00 and 7:30 a.m. on study day 1, control blood samples were obtained and the intravenous bolus dose of metoclopramide (10 mg) was given at 7:30 a.m. Blood samples were obtained at 10, 20, 30, 60, and 90 min (7:40, 7:50, 8:00, 8:30, and 9:00 a.m.) after metoclopramide administration. At 6:00 p.m. and midnight on study day 1, and at 6:00 a.m. on study day 2, bromocriptine 2.5 mg was administered orally. On study day 2, an identical protocol as for study day 1 was accomplished. On study day 2, to prevent any postural hypotension as a result of the treatment with bromocriptine, the subjects remained supine from the end of the study at 9:00 a.m. until noontime. Blood pressure was measured every 30 min with a mercury sphygmomanometer. The diet was discontinued and the subjects were discharged from the Clinical Research Center after completion of the final urine collection at 6:30 p.m. on study day 2. The total volume of blood obtained from each subject during the 2-d study was 320 ml.

During these studies, blood pressure was monitored with an Arteriosonde automatic ultrasonic blood pressure recorder. A blood pressure cuff (with a wide approximately two thirds of the width of the arm and a length sufficient for the bladder to completely encircle the arm) was wrapped snugly around the left arm. The Arteriosonde was calibrated daily against a random zero mercury sphygmomanometer. In the meto-

¹Abbreviation used in this paper: D_5W , 5% glucose solution.

cloramide/dopamine study, control blood pressure readings are expressed as the mean of 15 readings that were obtained between -120 and -90 min (6:30-7:00 a.m. = -90 control value) and between -90 and -60 min (7:00-7:30 a.m. = -60 control value) before administration of any intravenous pharmacological agents. After the control period, blood pressures are expressed as the mean of 15 readings for each 30-min period or as the mean of 5 readings for each 10-min period, as applicable. In the metoclopramide/bromocriptine study, control blood pressure readings are expressed as the mean of 15 readings between -30 and 0 min (7:00-7:30 a.m. = zero control value) before administration of any intravenous pharmacological agents. Metoclopramide was provided by A. H. Robins Co., Richmond, Va. Bromocriptine (CB154) was provided by Sandoz Pharmaceuticals Div., Hanover, N. J. Dopamine hydrochloride (Intropin) was supplied by Arnar-Stone Laboratories, Inc., Mount Prospect, Ill.

Analytical methods. All blood samples were collected in tubes on ice, centrifuged immediately, and the plasma was separated and frozen until time for assay. Samples for plasma renin activity and aldosterone used EDTA as the anticoagulant; heparin was used in the samples for cortisol.

Serum sodium and potassium levels were measured by flame photometry (model 143; Instrument Laboratories, Inc., Watertown, Mass.). Plasma aldosterone was measured by the method of Bühler et al. (17). After incubation, plasma renin activity was determined by radioimmunoassay of angiotensin I generated as described by Sealey et al. (18). Plasma cortisol was measured by specific radioimmunoassay (19). Serum prolactin was measured by the method of Sinha et al. (20).

Statistical analysis. Zero values obtained at 7:30 a.m. were used as control values for statistical comparisons. The results are expressed as mean \pm 1 SE. Statistical analysis was carried out with the double-tailed *t* test for paired data, and *P* values of <0.05 were considered significant.

RESULTS

Characteristics of the subjects before the metoclopramide/dopamine and metoclopramide/bromocriptine studies. The characteristics of the subjects in

sodium balance on the 5th d of normal sodium intake (150 meq/d) before each set of experiments are summarized in Table I. The 24-h urinary sodium and potassium excretion closely matched intake. No differences in the two groups of study subjects were present with respect to weights, urinary sodium, or potassium excretion, serum sodium or potassium concentrations, plasma renin activity or cortisol concentrations. However, the basal blood pressures and aldosterone values differed significantly among the experimental studies.

Metoclopramide/dopamine (2 μ g/kg per min) studies. Responses to metoclopramide in the presence of dopamine 2 μ g/kg per min and vehicle for five subjects are illustrated in Fig. 1. Blood pressures are shown in the left-hand panel. Vehicle infusion was associated with an increase in blood pressure (*P* < 0.05) at 0 min just before metoclopramide administration. In response to metoclopramide, there was no further change in blood pressure from the zero control value, and after discontinuation of the vehicle infusion at 60 min, blood pressure remained unchanged. Dopamine (2 μ g/kg per min) infusion was associated with a slight but significant (*P* < 0.05) increase in pulse pressure. Blood pressure was unchanged by metoclopramide or by subsequent discontinuation of dopamine. At no time point during the study was any value for systolic or diastolic blood pressure significantly different on the dopamine study day compared with the vehicle study day.

Plasma aldosterone concentrations are shown in Fig. 1, middle panel. In response to vehicle infusion, plasma aldosterone concentrations were unchanged. In response to metoclopramide, aldosterone concentrations increased at 10 min and further increased (*P* < 0.01) at 60 min. After discontinuation of vehicle, plasma aldosterone levels decreased slightly but remained above the zero control value for the remaining 60 min

TABLE I
Characteristics of the Subjects on the 5th d of Constant Normal Sodium Diet before the Metoclopramide/Dopamine and Metoclopramide/Bromocriptine Studies

	Metoclopramide/dopamine 2 μ g/kg/min	<i>P</i> *	Metoclopramide/dopamine 4 μ g/kg/min	Metoclopramide/ bromocriptine studies
Weight, kg	77.1 \pm 4.3	NS	76.4 \pm 3.8	76.8 \pm 5.2
24-h Urinary sodium, meq	154.8 \pm 9.7	NS	146.3 \pm 10.2	152.7 \pm 10.0
24-h Urinary potassium, meq	61.0 \pm 5.8	NS	63.7 \pm 4.8	65.5 \pm 7.3
Serum sodium, meq/liter	139.4 \pm 0.3	NS	139.8 \pm 4.8	140.1 \pm 0.4
Serum potassium, meq/liter	3.6 \pm 0.1	NS	3.7 \pm 0.1	3.7 \pm 0.1
Blood pressure, mm Hg				
Systolic	116.6 \pm 4.3	<0.05	122.1 \pm 2.9	108.0 \pm 2.0
Diastolic	76.8 \pm 1.1	<0.05	72.7 \pm 4.1	69.4 \pm 1.9
Plasma renin activity, ng/ml/h	2.5 \pm 0.4	NS	2.3 \pm 0.3	3.5 \pm 0.9
Plasma aldosterone, ng/100 ml	5.5 \pm 1.0	<0.05	2.6 \pm 0.8	9.9 \pm 2.7
Plasma cortisol, μ g/100 ml	13.2 \pm 0.8	NS	12.6 \pm 0.7	11.4 \pm 0.5

* *P* values indicate differences between metoclopramide/dopamine 2- and 4- μ g/kg/min studies in the same subjects.

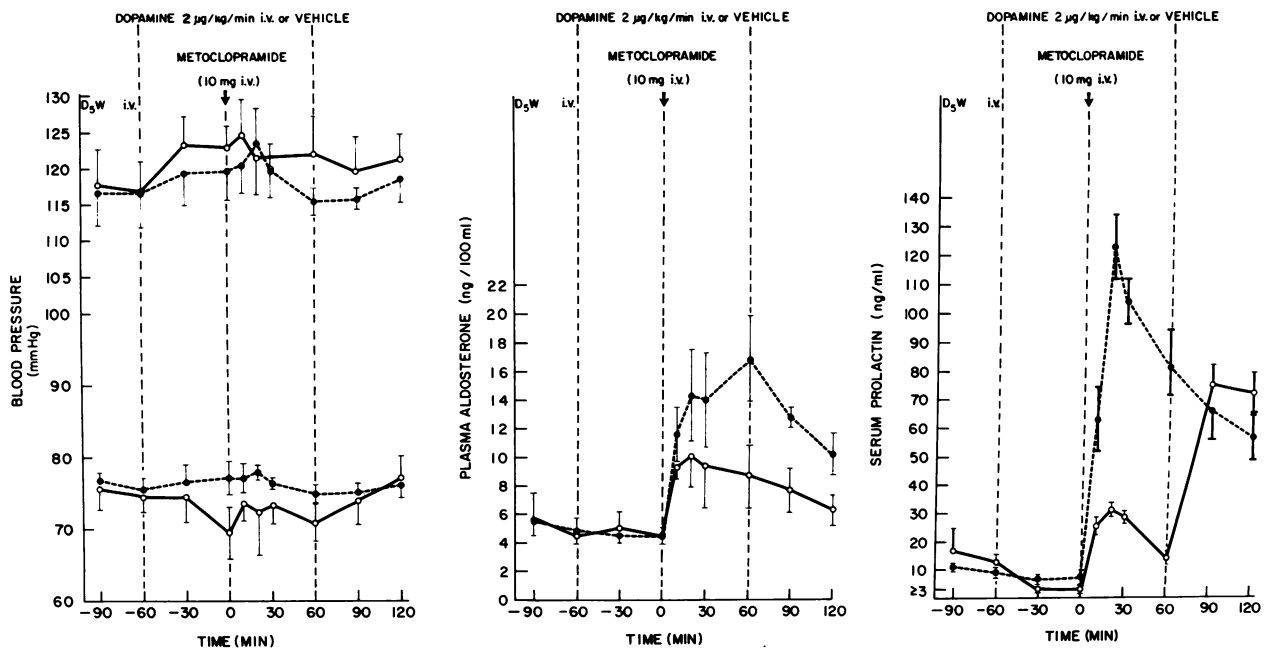


FIGURE 1 Blood pressure, aldosterone, and prolactin responses to metoclopramide 10 mg i.v. in five normal subjects (mean \pm SE). Dashed lines and solid circles represent data for study day one (vehicle infusion). Solid lines and open circles represent data for study day two (dopamine 2 μ g/kg per min infusion). Metoclopramide-induced increases in plasma aldosterone and serum prolactin concentrations were inhibited significantly by dopamine 2 μ g/kg per min.

of study. Aldosterone responses to metoclopramide were inhibited by dopamine 2 μ g/kg per min. There was no change in basal aldosterone in response to dopamine. Plasma aldosterone concentrations increased ($P < 0.01$) at 10 min after metoclopramide, then decreased gradually. The incremental aldosterone responses to metoclopramide were significantly lower with dopamine than with vehicle infusion only at 30 and 60 min after metoclopramide administration ($P < 0.01$). After discontinuation of dopamine, aldosterone levels continued to decrease gradually.

Serum prolactin concentrations are shown in Fig. 1, right-hand panel. Prolactin values were lower ($P < 0.05$) at -60 min than at -90 min of the control period before vehicle infusion. At -30 min during vehicle infusion, serum prolactin levels decreased further ($P < 0.05$), then remained stable. Metoclopramide administration increased prolactin values ($P < 0.005$) at 10 min and to a peak value ($P < 0.001$) at 20 min. Thereafter, prolactin concentrations decreased steadily. Dopamine (2 μ g/kg per min) significantly inhibited basal serum prolactin levels and the prolactin response to metoclopramide. Dopamine decreased serum prolactin concentrations significantly ($P < 0.01$); the zero control prolactin was < 3.0 ng/ml. In response to metoclopramide, there was an increase in serum prolactin concentration ($P < 0.01$) at 10 min, a

further increase at 20 min, followed by a decrease out to 60 min. However, the prolactin response to metoclopramide was smaller with dopamine than with vehicle at every time point ($P < 0.01$). After discontinuation of dopamine, prolactin concentrations increased within 30 min (90 min of study) to values not significantly different from those on the vehicle study day.

Metoclopramide/dopamine (4 μ g/kg per min) studies. Responses of the same subjects to metoclopramide in the presence of dopamine 4 μ g/kg per min or vehicle are shown in Fig. 2. Blood pressures are shown in the left-hand panel. Blood pressures did not change significantly in response to vehicle infusion. In response to metoclopramide administration, blood pressures increased ($P < 0.05$) at 10 min and remained elevated at 20 min; after this, blood pressures decreased toward control values and remained at control with discontinuation of vehicle infusion at 60 min. Dopamine (4 μ g/kg per min) infusion was associated with an increase in systolic blood pressures at -30 min ($P < 0.05$) and at 0 min ($P < 0.05$). In response to dopamine, the diastolic blood pressures remained unchanged at -30 min, but decreased ($P < 0.01$) at 0 min. Mean arterial blood pressures (diastolic plus one third of the pulse pressure) were not altered by dopamine. Metoclopramide administered concomitantly with dopamine did not affect significantly systolic or

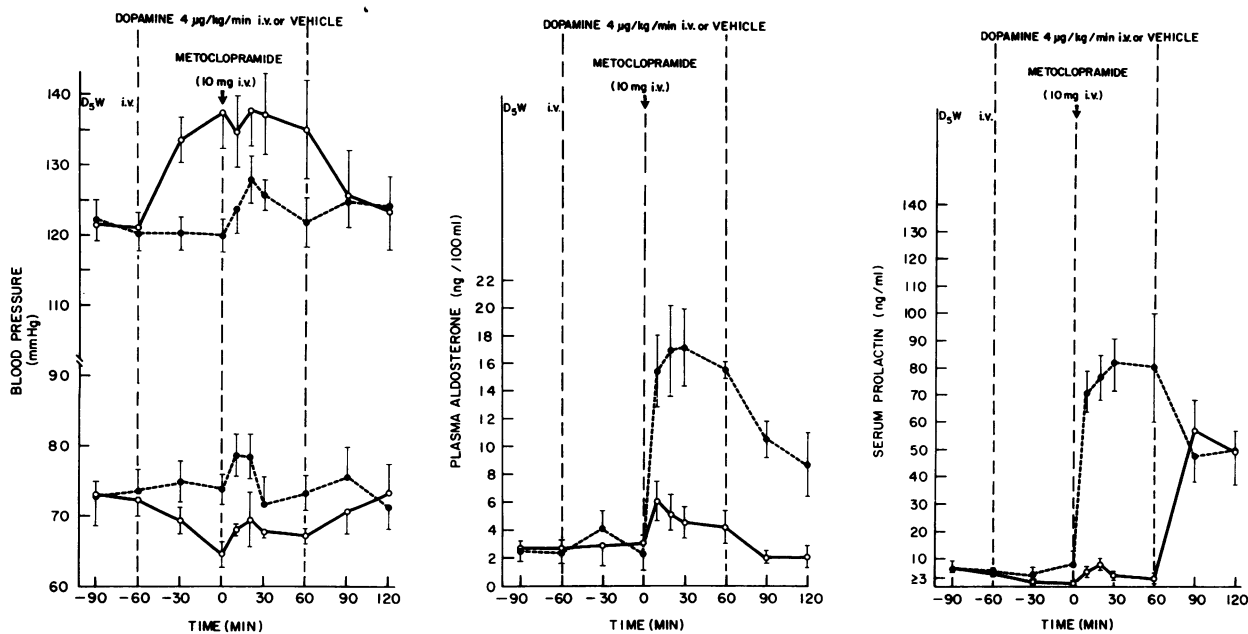


FIGURE 2 Blood pressure, aldosterone, and prolactin responses to metoclopramide 10 mg i.v. in five normal subjects (mean \pm SE). Dashed lines and solid circles represent data for study day one (vehicle infusion). Solid lines and open circles represent data for study day two (dopamine 4 μ g/kg per min infusion). Metoclopramide-induced increases in plasma aldosterone and serum prolactin concentrations were inhibited significantly by dopamine 4 μ g/kg per min.

diastolic blood pressures, which returned to control values after discontinuation of the dopamine infusion at 60 min.

Plasma aldosterone concentrations are shown in Fig. 2, middle panel. Vehicle infusion did not alter the plasma aldosterone concentrations significantly. Metoclopramide administration produced an increase in plasma aldosterone concentrations ($P < 0.01$) at 10, 20, and 30 min. These increases in aldosterone concentrations were followed by progressive decreases at 60, 90, and 120 min of study. Dopamine (4 μ g/kg per min) inhibited the aldosterone responses to metoclopramide. Dopamine infusion produced no significant changes in basal aldosterone concentrations. In response to metoclopramide in the presence of dopamine, aldosterone levels increased ($P < 0.05$) at 10 min after metoclopramide, then progressively decreased toward the control values at zero time. In the presence of dopamine (4 μ g/kg per min), incremental aldosterone responses to metoclopramide were significantly lower than with vehicle at 10 min ($P < 0.01$), 20 min ($P < 0.05$), 30 min ($P < 0.01$), and 60 min ($P < 0.01$). After discontinuation of the dopamine infusion at 60 min, aldosterone concentrations decreased further to control values.

The incremental responses of plasma aldosterone concentration to metoclopramide in the presence of "vehicle" for dopamine 2 μ g/kg per min and 4 μ g/kg per min were 12.5 ± 1.7 and 14.8 ± 2.0 ng/100 ml ($P = \text{NS}$),

respectively. In contrast, the incremental aldosterone responses to metoclopramide in the presence of dopamine 4 μ g/kg per min, 3.1 ± 0.9 ng/100 ml, were significantly lower than in the presence of dopamine 2 μ g/kg per min, 5.0 ± 0.8 ng/100 ml ($P < 0.05$).

Serum prolactin concentrations are shown in Fig. 2, right-hand panel. Vehicle infusion was not associated with any significant change in serum prolactin concentrations. Metoclopramide increased prolactin levels ($P < 0.01$) at 10 min and to a peak value ($P < 0.01$) at 30 min. Prolactin concentrations were still elevated at 60 min, but decreased at 90 min (40 min after cessation of vehicle infusion). Dopamine (4 μ g/kg per min) decreased basal prolactin levels and inhibited the prolactin response to metoclopramide. After 30 min of dopamine infusion, prolactin had decreased to undetectable levels (< 3 ng/ml) and remained suppressed at 0 min before metoclopramide administration. There was a peak increase of serum prolactin concentrations ($P < 0.05$) at 20 min in response to metoclopramide, but at 60 min the prolactin was just barely detectable. After the discontinuation of the dopamine infusion, there was a marked increase of serum prolactin concentrations ($P < 0.01$).

During the metoclopramide/dopamine studies at both dose levels of dopamine, there were no changes in plasma renin activity, plasma cortisol, serum sodium, or potassium concentrations in response to metoclopramide, dopamine, or vehicle (data not shown).

Metoclopramide/bromocriptine study (Fig. 3). Supine blood pressures of the remaining five subjects are depicted in Fig. 3, left-hand panel. The -30 control values for blood pressure were similar after placebo and bromocriptine administration, but the zero control values for systolic and diastolic pressure were lower after bromocriptine than placebo ($P < 0.05$). In response to metoclopramide, there was no change in blood pressure after placebo or bromocriptine administration from respective zero control values.

Plasma aldosterone concentrations are shown in Fig. 3, middle panel. In response to metoclopramide, plasma aldosterone concentrations increased ($P < 0.05$) at 10 min and remained elevated from control values for 90 min. Control aldosterone values after placebo and bromocriptine were similar. After bromocriptine, metoclopramide increased aldosterone concentrations ($P < 0.05$) at 10 min, and aldosterone remained elevated for the duration of the study. No significant differences in aldosterone values were observed in response to metoclopramide whether the subjects were pretreated with placebo or bromocriptine.

Serum prolactin concentrations are shown in Fig. 3,

right-hand panel. At 10 min after metoclopramide administration, serum prolactin levels increased ($P < 0.005$). Serum prolactin increased further ($P < 0.001$) at 30 min after metoclopramide and remained elevated for the remainder of the study period. Bromocriptine consistently suppressed serum prolactin concentrations to < 3 ng/ml ($P < 0.001$) and metoclopramide failed to increase prolactin in bromocriptine-treated subjects.

Concentrations of plasma cortisol, serum sodium, and potassium, and plasma renin activity did not change significantly at any time during the metoclopramide/bromocriptine studies (data not shown).

DISCUSSION

The present investigation was designed to determine the effects of dopamine agonists on metoclopramide-induced aldosterone secretion in normal man. Two agonists, dopamine and bromocriptine, were selected for study. The first agent, bromocriptine, is an ergot derivative and was developed by Flückiger and Wagner as an inhibitor of pituitary prolactin secretion

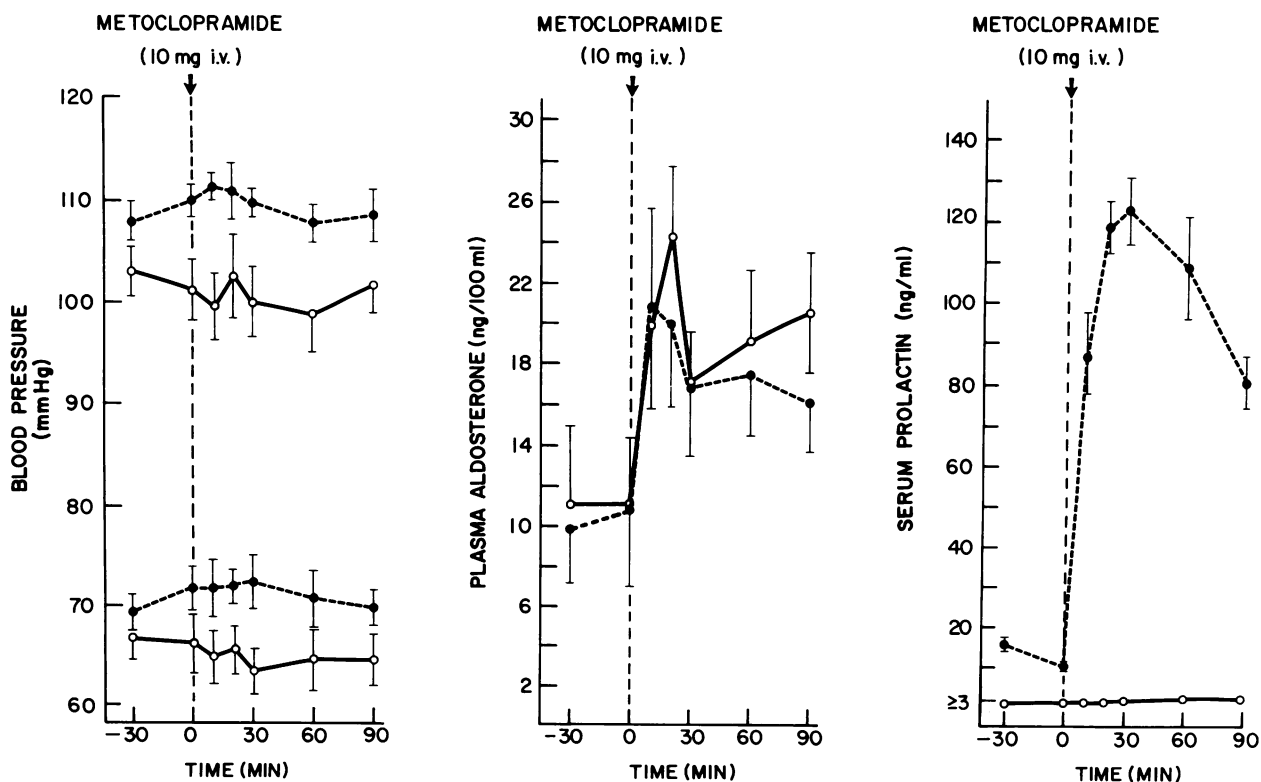


FIGURE 3 Blood pressure, aldosterone, and prolactin responses to metoclopramide 10 mg i.v. in five normal subjects (mean \pm SE). Dashed lines and solid circles represent data for study day one (placebo for bromocriptine). Solid lines and open circles represent data for study day two (bromocriptine). Although metoclopramide-induced increases in serum prolactin concentrations were inhibited significantly by bromocriptine, metoclopramide-induced increases in plasma aldosterone concentrations were not altered by bromocriptine.

(21). However, the mechanism of action of bromocriptine was determined later to be a prolonged dopaminergic response (22–24). Bromocriptine acts as a dopamine agonist in the central nervous system (22, 23), at the pituitary gland to inhibit prolactin release (14, 25–27), and on peripheral vascular dopamine receptors to produce vasodilatation of renal and mesenteric arteries (28). Bromocriptine has been demonstrated to bind to dopamine receptors in radio-receptor assays using membranes from brain homogenates (29). Bromocriptine also is a weak alpha-adrenergic and serotonergic antagonist, but it is unlikely that these actions would mediate the observed changes because low doses were used in the present studies (23). The other agent used in these studies was dopamine, a precursor of the sympathetic neurotransmitter, norepinephrine. Dopamine is possibly a major transmitter of the peripheral autonomic nervous system (30). Although dopamine possesses weak alpha- and beta-adrenergic activities, in the quantities employed here little or no adrenoreceptor effects would be expected to occur (31). Furthermore, there is no precedent for suppression of aldosterone secretion by sympathomimetic agents. The dopaminergic antagonist, metoclopramide, and the dopaminergic agonists, bromocriptine and dopamine, employed in these studies were chosen because of their relative selectivity for dopamine receptors, but it is recognized that no pharmacological agent is completely specific.

This investigation demonstrated that dopaminergic mechanisms affect the adrenal gland as evidenced by a maximum tonic inhibitory influence on aldosterone production in man. Basal plasma aldosterone concentrations were not decreased by the administration of dopamine. However, metoclopramide-induced increases in plasma aldosterone concentration were inhibited by dopamine. Although this effect could be related to some indirect effect of dopamine, this possibility seems unlikely. None of the known mediators of aldosterone secretion changed during the administration of metoclopramide alone or in the presence of dopamine. Although complete obliteration of the aldosterone response to metoclopramide was not achieved even with the highest dose of dopamine employed, the inhibition of metoclopramide-induced increases in plasma aldosterone concentration by dopamine was dose-dependent with the larger quantity of dopamine inhibiting the aldosterone response more completely. These results strongly suggest that the aldosterone response to metoclopramide is mediated by an antagonist activity at dopamine receptors.

Unexpectedly, metoclopramide-induced increases in plasma aldosterone concentration were not inhibited by bromocriptine. In fact, the aldosterone responses to metoclopramide were virtually identical at all time points from 0 to 90 min after administration

of bromocriptine or its placebo. This observation may explain our previous finding (16) that bromocriptine did not inhibit the adrenal steroidogenic response to angiotensin II. A possible explanation for this finding might be that bromocriptine acts as a renal vasodilator, stimulating renin release and, thus, augmenting aldosterone secretion. However, the absence of change in plasma renin activity with bromocriptine administration virtually excludes this mechanism.

The finding that metoclopramide-induced aldosterone production is inhibited by dopamine but not by bromocriptine raises interesting questions concerning the pharmacological characteristics of putative dopamine receptors in the adrenal zona glomerulosa as compared with those in the pituitary gland. The efficacy of the dopamine agonists and antagonist used in this study on pituitary dopamine receptors was monitored by means of changes in serum prolactin concentration. In response to metoclopramide, serum prolactin concentrations increased markedly. Dopamine decreased basal prolactin to levels below detection limits of our assay and inhibited prolactin responses to metoclopramide in a dose-dependent manner with nearly complete inhibition at 4 $\mu\text{g}/\text{kg}$ per min. Similarly, bromocriptine decreased basal prolactin below detectable limits and obliterated the prolactin response to metoclopramide. Thus, the pituitary dopamine receptor was inhibited by both dopamine and bromocriptine, whereas only dopamine was effective on the adrenal response.

Recently, Kebejian and Calne (32) have reviewed evidence for different classes of dopamine receptors in various tissues. At least two categories of dopamine receptors can be identified on the basis of biochemical criteria. One type of dopamine receptor, termed D-1, is linked to adenylate cyclase; stimulation of this receptor results in accumulation of intracellular cyclic AMP. Renal vascular dopamine receptors are examples of D-1 receptors. The other type of dopamine receptor, designated as D-2, is not adenylate cyclase-linked; pituitary lactotrophs are prototype cells containing D-2 receptors.

The results of the present studies are not consistent with either of these two subclasses of dopaminergic receptors. The receptors mediating the adrenal response are probably not D-2 because bromocriptine, a pituitary D-2 receptor agonist, did not inhibit the aldosterone response to metoclopramide. Because dopamine itself is an agonist at both D-1 and D-2 receptors, inhibition of metoclopramide-induced aldosterone production by dopamine does not indicate conclusively which receptor class is involved. However, it should be noted that dopamine agonists may have a differential effect on D-1 or D-2 receptors based on quantitative considerations. Relatively large amounts (micromolar concentrations) of dopamine are required

to stimulate D-1 receptors compared with the relatively smaller quantities (nanomolar concentrations) required for stimulation of D-2 receptors. In the present study, on the basis of the dose-related inhibitory effects of dopamine to suppress prolactin, we postulate that we are dealing with nanomolar quantities of dopamine. We gave almost maximal amounts of dopamine for inhibition of prolactin release, and thus for stimulation of D-2 receptors. This quantity of dopamine would be insufficient to stimulate D-1 receptors; therefore, the receptors controlling aldosterone cannot be characterized exclusively as D-1. Some of the ergot dopamine agonist derivatives have been described to possess antagonist properties for the D-1 receptor; at the dose used in the present study, bromocriptine cannot be acting in this manner because bromocriptine did not stimulate basal aldosterone secretion.

Our results present *in vivo* evidence of dissociation of responses to dopamine agonists in man. Levodopa, dopamine, and the dopaminergic ergots elicit similar biological responses in Parkinsonism (33, 34) or in the suppression of prolactin, as demonstrated in this study, but not in the control of aldosterone secretion. Our data further suggest that a new type of dopamine receptor may inhibit aldosterone secretion. This hypothesis is in keeping with the suggestion of Keabian and Calne (32) that new categories or sub-categories of dopamine receptors may be identified on the basis of pharmacological evidence. Studies of the effect of pretreatment with a wide range of dopamine receptor agonists on the aldosterone response to sodium deprivation, angiotensin II, ACTH, and a variety of dopamine antagonists will help define more clearly the specific dopamine receptor mechanism involved in the control of aldosterone secretion.

The contrast between the patterns of prolactin and aldosterone response to cessation of the dopamine infusions deserves mention. Serum prolactin concentrations increased within 30 min of dopamine withdrawal to markedly elevated values similar to those after metoclopramide administration alone. However, plasma aldosterone concentrations remained suppressed up to 60 min after discontinuation of dopamine. The findings could be related to (a) increased sensitivity of prolactin- compared with aldosterone-secreting cells to dopamine's acute inhibitory influence, (b) prolonged interaction of dopamine with dopamine receptors on aldosterone secreting cells, and (c) other unknown homeostatic mechanisms controlling aldosterone secretion.

Although we have demonstrated that metoclopramide acts by antagonizing the tonic inhibition by dopamine of aldosterone secretion, its exact mechanism of action on the adrenal zona glomerulosa remains to be elucidated. Recent *in vitro* studies have demonstrated that dopamine inhibits the aldosterone

secretory response to angiotensin II in suspensions of bovine adrenal zona glomerulosa cells (35). Basal aldosterone secretion was unaltered by dopamine. This evidence suggests that metoclopramide may act directly at the adrenocortical cellular level by antagonizing dopaminergic inhibition of aldosterone secretion. However, studies demonstrating dopamine receptors in adrenal glomerulosa cells and specific binding of dopamine antagonists to these cells will be required to clarify the precise nature of dopaminergic inhibition of aldosterone secretion.

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