Dopamine during α- or β-Adrenergic Blockade in Man

HORMONAL, METABOLIC, AND CARDIOVASCULAR EFFECTS

MARA LORENZI, JOHN H. KARAM, EVA TSALIKIAN, NANCY V. BOHANNON, JOHN E. GERICH, and PETER H. FORSHAM, *Metabolic Research Unit and Department of Medicine, University of California, San Francisco, San Francisco, California 94143*

ABSTRACT We studied the contribution of α- and β-adrenergic receptor activation to the cardiovascular, metabolic, and hormonal effects of dopamine. At a concentration of 1.5 μg/kg·min, the infusion of dopamine in 12 normal volunteers was associated with a transient but significant rise in pulse rate, which was prevented by propranolol. Venous plasma glucose did not change throughout the experiments, and a mild increase in plasma free fatty acid levels observed during the administration of dopamine alone was antagonized by propranolol. In contrast, neither the β-adrenergic blocker, propranolol, nor the α-adrenergic blocker, phentolamine, was effective in inhibiting the dopamine-induced rise in plasma glucagon (from 82±9 to 128±14 pg/ml; $P < 0.005$) and serum insulin (from 7.5±1 to 13±1.5 μU/ml; $P < 0.005$) or its suppression of plasma prolactin (from 8.5±1 to 5.2±0.8 ng/ml; $P < 0.001$). Although serum growth hormone levels did not change during the infusion of dopamine alone, an obvious rise occurred in three subjects during the combined infusion of propranolol and dopamine.

Whereas some metabolic and cardiovascular effects of dopamine are mediated through adrenergic mechanisms, these observations indicate that this is not the case for the effects of this catecholamine on glucagon, insulin, and prolactin secretion, and thus provide further support for the theory of a specific dopaminergic sensitivity of these hormonal systems in man.

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INTRODUCTION

Dopamine, the immediate precursor of norepinephrine in chromaffin tissue and noradrenergic nerves, is present in several other organs and tissues with an asymmetric distribution relative to norepinephrine (1, 2). Dopamine is also detected in blood in concentrations similar to, or exceeding, those of norepinephrine (3). It is tempting to speculate that peripheral dopamine might subserve functions different from the ones ascribed to the other two naturally occurring catecholamines, because adrenergic nervous activity does not seem to contribute to its circulating levels (3) and several cardiovascular and renal effects of dopamine cannot be simulated by norepinephrine or epinephrine (4). The secretion of polypeptide hormones is readily affected by dopamine: inhibition of prolactin release is well documented in vivo (5, 6) and in vitro (7); the growth hormone secretory system is responsive to dopaminergic agents (8, 9); and both glucagon and insulin release are stimulated by dopamine (10), as are renin (11) and parathyroid hormone (12). With the exception of prolactin secretion (13, 14), however, no physiologic role has hitherto been attributable to dopamine in the regulation of these endocrine systems, nor has it been established in man that the above hormonal responses are mediated through the interaction of dopamine with receptors different and independent from the well-described adrenergic receptors. A better pharmacologic characterization of the endocrine effects of dopamine is warranted in view of the multireceptor potential of the dopamine molecule (15). We have examined at this time the interactions of dopamine with α- and β-adrenergic receptors in mediating changes in circulating glucagon, insulin, prolactin, and growth hormone levels in man.

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METHODS

12 normal subjects (3 women and 9 men), aged 25–30 yr, volunteered for the studies, which were performed after an overnight fast between 8 and 11 a.m. in outpatient facilities of the Metabolic Research Unit, University of California, San Francisco, San Francisco, Calif. All 12 subjects underwent a study with dopamine alone; 5 of them (all men) were subsequently studied with dopamine and a β-blocker and, on another day, with dopamine and an α-blocker. Because one subject experienced side effects during the α-blocker experiment that necessitated its termination, a sixth subject underwent the dopamine and α-blocker study.

A 19-gauge butterfly needle was inserted in an antecubital vein of the left arm for blood sampling and maintained patent through an infusion of 0.9% saline solution. A mercury sphygmomanometer was placed on the same arm for blood pressure monitoring. A 21-gauge butterfly needle was inserted in a forearm vein of the right arm for drug administration, likewise kept patent with an infusion of 0.9% saline solution.

At least 30 min of bed rest were allowed before obtaining base-line samples. In all experiments blood samples were obtained, at intervals specified below, for the determination of plasma glucose, free fatty acid (FFA),[1] glucagon, insulin, prolactin, and growth hormone levels. Blood pressure and pulse rate were monitored throughout the procedures and recorded before each blood sampling. In the studies with dopamine alone, all determinations were obtained 30 min and immediately before (time 0) the initiation of the infusion, then every 10 min during the 60-min infusion period, and at 15-min intervals for the 30 min after discontinuation of the infusion. Dopamine was administered over 60 min in a concentration of 1.5 μg/kg·min, which is lower that that used by other investigators for endocrine studies (6, 10). The rate of dopamine infusion was chosen on the basis of effectiveness and safety: typical dopaminergic effects on renal blood flow in man are elicited by doses between 1 and 2 μg/kg·min (16), whereas only concentrations in excess of 3 μg/kg·min have been reported to induce subjective and objective symptoms (17). A constant rate of infusion was ensured by the use of a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) delivering the predetermined fraction of a 0.1% solution of dopamine hydrochloride (Intropin; Arnar-Stone Laboratories, Inc., Mt Prospect, Ill.) (20 mg diluted in 20 ml of 0.9% saline solution).

In the experiments with adrenergic blockers, base-line determinations were obtained at −60 and −30 min. The infusion of the α- or β-adrenergic blocker was then started (−30 min) and 2 samples were obtained at 15-min intervals (−15 and 0 min). At 0 time the infusion of dopamine was initiated, and samples were thereafter obtained as described for the experiments with dopamine alone. Propranolol (Inderal; Ayerst Laboratories, New York) was used as the β-blocker, and 7.2 mg were diluted in 35 ml of 0.9% saline solution and delivered at a rate of 0.08 mg/min for a total of 90 min by a second Harvard pump connected, with the one delivering dopamine, to the intravenous infusion line in the right arm of the subject. The α-blocker used was phentolamine (Regitine; Ciba Corp., Summit, N. J.); 45 mg were diluted as for propranolol and delivered at a rate of 0.5 mg/min for a total of 90 min by the procedure described above.

Plasma glucose levels were determined by a glucose oxidase method using an oxygen electrode (18), and plasma FFA by a colorimetric micromethod (19). Serum insulin (20), serum growth hormone (21), and plasma prolactin (22) levels were determined by previously described radioimmunoassays. Plasma glucagon was also determined by radioimmunoassay (23) using antiserum 30K, which has been reported to react with heterogeneous species of glucagon (24).

Results are expressed as the mean±SE. The data were analyzed for statistical significance by means of the two-tailed, paired Student's *t* test.

RESULTS

Dopamine studies

Cardiovascular and other side effects. During the infusion of dopamine alone (1.5 μg/kg·min), a minimal increment in pulse rate was observed during the first 20 min (from 62±2.1 to 67±2 beats/min). This change was statistically significant ($P < 0.05$). The pulse rate stabilized thereafter at an average of 65±2 and returned to 60 beats/min 30 min after discontinuation of the infusion. No appreciable changes in blood pressure or other side effects were observed, except for a symptomatic hypotensive episode in one woman a few minutes after initiation of the dopamine infusion. This subject became diaphoretic, nauseated, and tachycardic, and the infusion was immediately terminated. Prompt recovery ensued.

Plasma glucose, FFA, insulin, and glucagon responses (Fig. 1). Plasma glucose values remained essentially unchanged during the study, whereas FFA levels gradually increased from 0.54±0.06 to 0.63±0.07 meq/liter at the end of the dopamine infusion ($P < 0.02$) and continued to rise in the 30 min after discontinuation. Serum insulin values rose from 7.5±1 to a peak of 13±1.5 μU/ml ($P < 0.005$) 20 min after initiation of dopamine and stabilized at a plateau of 10.5 μU/ml during the last 30 min of infusion. The values recorded at 40, 50, and 60 min were significantly lower than those observed at 20 and 30 min ($P < 0.005$), but they were still different from base line ($P < 0.005$).

A similar pattern was observed for plasma glucagon, which increased from 82±9 to 128±14 pg/ml ($P < 0.005$) only 10 min after initiation of the dopamine infusion and declined to an average of 108±10 pg/ml during the last 30 min of infusion.

For both insulin and glucagon, a rapid return to base-line values followed the termination of dopamine administration.

Growth hormone and prolactin responses (Fig. 2). Serum growth hormone levels did not change significantly in the group of subjects studied. Plasma prolactin levels were progressively lowered by dopamine from 8.5±1 to 5.2±0.8 ng/ml ($P < 0.005$). During the 30 min after discontinuation of the infusion, prolactin levels returned toward base line although they were still somewhat suppressed.

Dopamine and propranolol studies

Cardiovascular and other side effects. In the five subjects studied, dopamine alone had increased pulse

[1] *Abbreviation used in this paper:* FFA, free fatty acids.

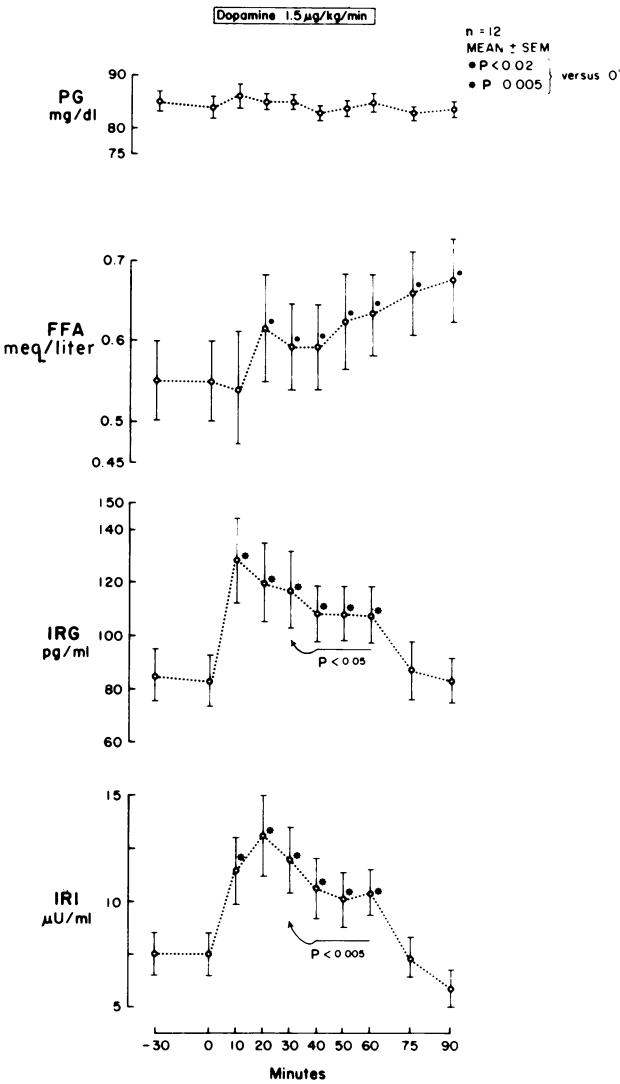

FIGURE 1 Effect of dopamine infusion on circulating plasma glucose (PG), FFA, and immunoreactive glucagon (IRG) and insulin (IRI). The arrows indicate comparison of the values obtained at 40, 50, and 60 min with the 30-min value.

rate from 59±1.4 to 66±4 beats/min ($P < 0.05$) by 10 min after initiation of the infusion. In the experiments with propranolol, the pulse rate, which had decreased from 58±3 to 53±4 beats/min ($P < 0.01$) after 30 min of propranolol alone, did not show any rise upon addition of dopamine. No changes in blood pressure or other side effects were observed.

Plasma glucose, FFA, insulin, and glucagon responses (Fig. 3). Neither plasma glucose nor FFA levels changed appreciably throughout the administration of propranolol and dopamine (not shown). With regard to the FFA levels, this was in contrast to the significant rise observed during the infusion of dopamine alone in these five subjects.

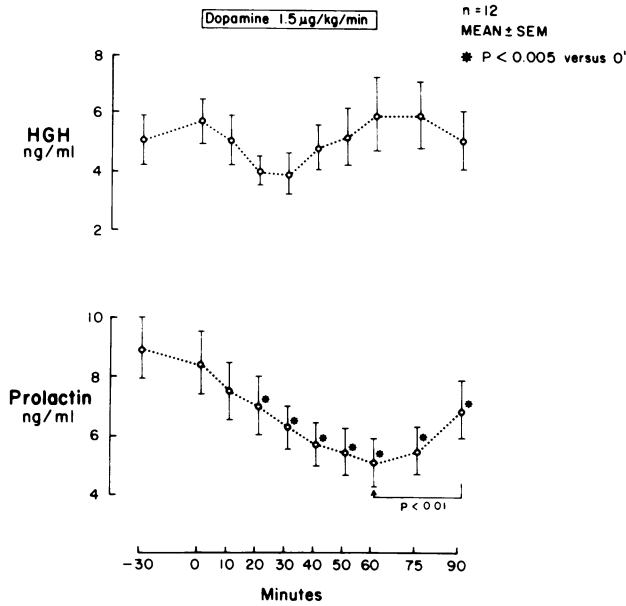

FIGURE 2 Effect of dopamine infusion on circulating human growth hormone (HGH) and prolactin levels. The arrow indicates a comparison between the prolactin values at 90 and 60 min.

Serum insulin levels decreased during the administration of propranolol alone from 11±2 to 8.5±2.5 µU/ml, but the change did not achieve statistical significance. Upon initiation of dopamine, the increment in serum insulin was indistinguishable from the one obtained in the control experiments.

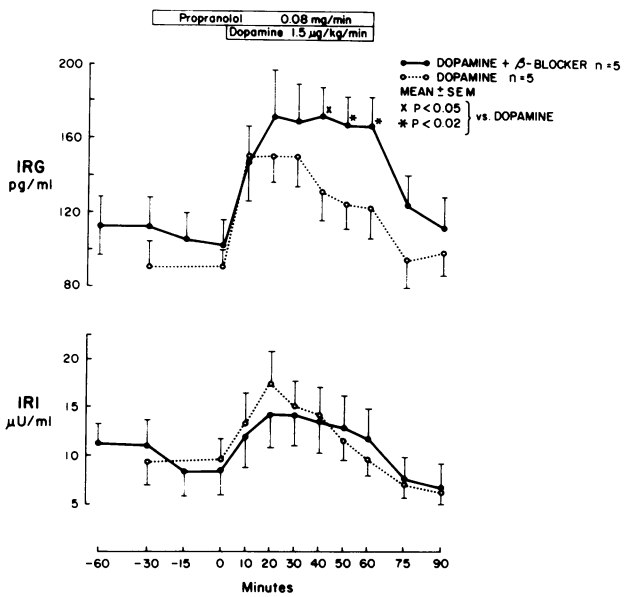

FIGURE 3 Effect of propranolol on circulating immunoreactive glucagon (IRG) and insulin (IRI) responses to dopamine infusion.

A similar pattern was observed for plasma glucagon: propranolol tended to suppress basal levels (from 115 ±20 to 104±15 pg/ml; NS) but did not affect the response to dopamine. During the last 30 min of infusion, however, plasma glucagon was significantly higher in the experiments with propranolol and dopamine ($P < 0.02$), with consequent obliteration of the biphasic pattern of response observed with dopamine alone.

Growth hormone and prolactin responses (Fig. 4). During the combined infusion of dopamine and propranolol, a growth hormone rise was observed in three subjects (respective peaks: 29, 19, and 13 ng/ml); in the other two, no detectable changes occurred. In none of the five was the dopamine-induced suppression of plasma prolactin levels affected by propranolol.

Dopamine and phentolamine studies

Cardiovascular and other side effects. The pulse rate had increased from 56±3 to 69±3 beats/min ($P < 0.01$) 30 min after the initiation of phentolamine. It further increased to an average of 75±4 ($P < 0.01$) during the infusion of dopamine. This increment was not different from the one observed with dopamine alone. Whereas the systolic blood pressure did not change appreciably in the supine position during the infusion of phentolamine and dopamine, the diastolic pressure decreased from 76±3 to 67±3 mm Hg ($P < 0.05$).

In one male subject, a symptomatic hypotensive episode occurred 2 min after the addition of dopamine to the phentolamine infusion although this same subject had tolerated a previous experiment with dopamine alone without any side effects. Upon immediate termination of the infusion, prompt recovery ensued.

All subjects experienced nasal stuffiness and increased lacrimal secretion. Some degree of orthostatic hypotension was present at the end of the experiment, and therefore the subjects were not allowed to leave until blood pressure had stabilized (generally 1 h after the end of the experiment).

Plasma glucose, FFA, insulin, and glucagon responses (Fig. 5). No appreciable changes in plasma glucose were observed. The plasma level of FFA, which had increased from 0.63±0.03 to 0.75±0.06 meq/liter during the infusion of phentolamine alone ($P < 0.05$), reached 0.93±0.1 meq/liter 10 min after the initiation of dopamine and stabilized thereafter at an average of 0.83 meq/liter. These levels were not statistically different from those observed during the administration of dopamine alone.

Serum insulin levels rose slightly during the administration of phentolamine alone from 7.4±1.7 to 8.6±1.6 μU/ml ($P < 0.05$). The insulin response to dopamine was not modified by the α-blocker. Phentolamine alone did not affect basal glucagon levels, nor did it impair the glucagon response to dopamine. The higher glucagon levels observed during the last 30 min of combined dopamine and phentolamine infusion were likely a consequence of the higher base-line values because no significant difference from the control study

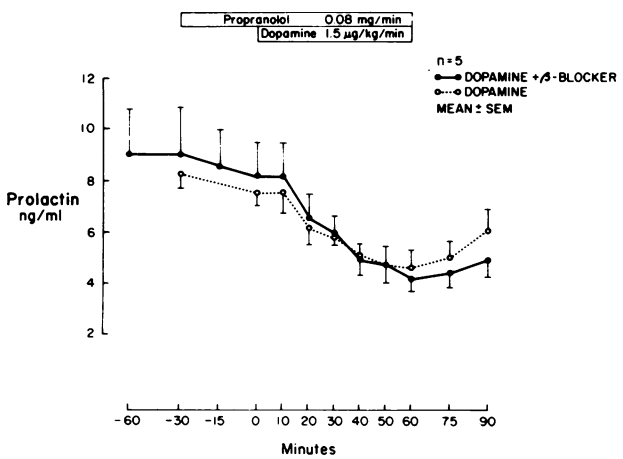

FIGURE 4 Effect of propranolol on the circulating prolactin response to dopamine infusion.

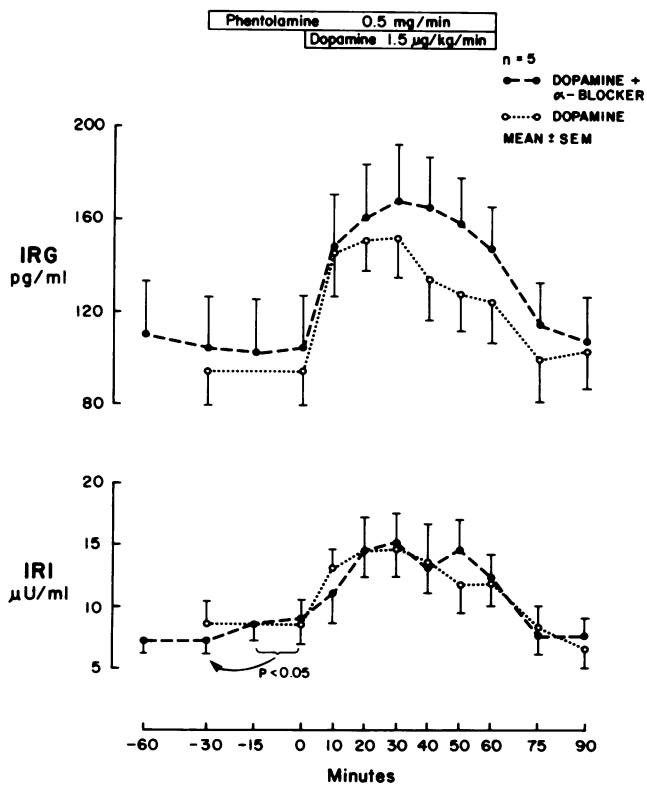

FIGURE 5 Effect of phentolamine on circulating immunoreactive glucagon (IRG) and insulin (IRI) responses to dopamine infusion. The arrow indicates comparison of the IRI value recorded at −30 min with those at −15 and 0 min.

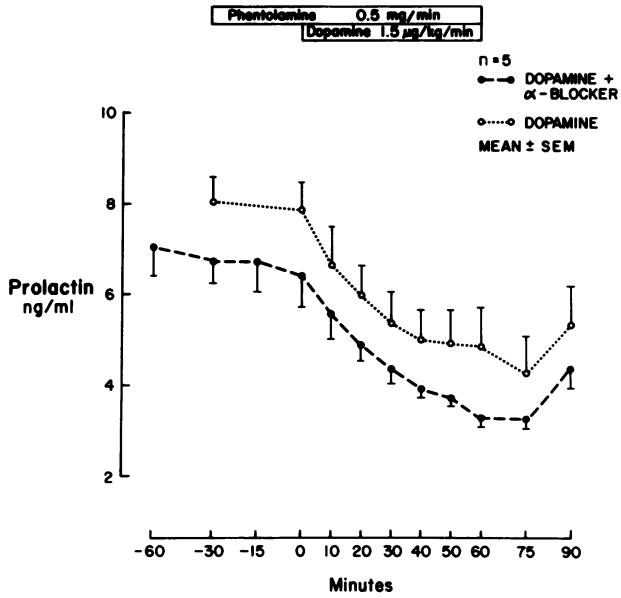

FIGURE 6 Effect of phentolamine on the circulating prolactin response to dopamine infusion.

could be detected when the responses were analyzed as increments from time 0.

Growth hormone and prolactin responses (Fig. 6). No changes were observed in serum growth hormone levels during the combined administration of dopamine and phentolamine. Phentolamine alone did not affect basal plasma prolactin levels, nor did it interfere with the dopamine-induced suppression.

DISCUSSION

The results of this study indicate that, in man, the effects of dopamine on certain endocrine glands are not antagonized by α- or β-adrenergic blockers. Although this finding is not equivalent to the identification of dopaminergic receptors on the secretory systems studied, it contributes further likelihood for their existence because adequate adrenergic blockade appears to have been achieved. The dose of propranolol used here had been observed to effect β-blockade against isoproterenol (25, 26), epinephrine (27), and norepinephrine (25). In our experiments, it fully antagonized the chronotropic and lipolytic effects of dopamine in accordance with the notion that this catecholamine's effect on heart rate involves activation of β-adrenergic receptors (4) and that the lipolytic action of catecholamines on adipose tissue is also predominantly mediated by β-receptors (28). The development of nasal stuffiness, increased lacrimal secretion, tachycardia, and orthostatic hypotension in all subjects receiving phentolamine was considered an appropriate indication of adequate α-adrenergic blockade. Moreover, the dose of phentolamine used had been reported to block cardiovascular and ventilatory responses to phenylephrine (25) and to antagonize epinephrine's effect on insulin secretion (29).

It therefore seems reasonable to assume that the effects of dopamine observed in the presence of the blockers were independent of activation of α- and β-adrenergic receptors. Furthermore, dopamine established its dissociation from epinephrine and norepinephrine by being almost totally ineffective upon systems exquisitely sensitive to these endogenous catecholamines. Despite the administration of dopamine at a dose 15 times greater than that at which epinephrine and norepinephrine cause hypertension and hyperglycemia (30), we did not observe increases in plasma glucose or blood pressure. With regard to the steady venous plasma glucose levels during dopamine infusion, we cannot exclude the possibility that arterial glucose increased, but glucose turnover was accelerated by the rise in insulin concentration. However, because isoproterenol induces venous hyperglycemia despite comparably enhanced insulin release (26), this explanation appears inadequate. An inferior glycogenolytic potency of dopamine is a likely possibility and should be verified in isolated organ studies.

In contrast with the chronotropic and lipolytic effect of dopamine, reversed by propranolol, the hormonal responses could not be antagonized by either adrenergic blocker. As far as glucagon is concerned, this finding provides further support for the hypothesized dopaminergic sensitivity of that secretory system based on observations in primates that the glucagon response to the dopamine precursor *l*-dopa is not antagonized by α- or β-adrenergic blockers (31). The potentiation of the glucagon response observed in this study during propranolol administration might be explained by the concurrent inhibition of the FFA rise insofar as these substrates are effective modulators of glucagon secretion (32).

If a positive glucagon response to dopamine is not surprising in view of the well-established stimulatory effect of catecholamines on this hormone (32), the elevated insulin level is at variance with its reported inhibition by the other two endogenous catecholamines (32). Moreover, in vitro studies have demonstrated that dopamine inhibits insulin release (33, 34) and that such inhibition is prevented by phentolamine (34). However, those studies differ from ours in many respects: experiments were carried out in vitro with pancreatic pieces from animal donors; insulin release was evaluated under stimulated conditions; and the concentrations of dopamine added to the incubation medium (10–100 μM) were immense in comparison with the local pancreatic concentrations that our rate of systemic infusion would have achieved. Under the above experimental conditions, activation of α-adrenergic receptors by dopamine might have occurred, with

consequent inhibition of insulin release and reversal of the effect by the α-blocker. Not having studied arterial glucose levels, we cannot exclude the possibilities that the rise in serum insulin may represent a response to some degree of hyperglycemia or may be a consequence of glucagon stimulation. Despite concomitant hyperglycemia and hyperglucagonemia, however, the other two endogenous catecholamines still produce insulin suppression through activation of α-adrenergic receptors (32). While the different effect of dopamine strongly militates against an interaction of this catecholamine with α-receptors, the inability of propranolol to antagonize the insulin response excludes an interaction of dopamine with stimulatory β-receptors. Therefore, it seems that dopamine has effects on pancreatic β-cells in man independent of conventional α- and β-adrenergic receptors.

All three natural catecholamines have been reported to interfere with prolactin secretion (7, 35, 36). The action of norepinephrine is antagonized by either α- or β-adrenergic blockers (35), and the dopamine-induced suppression is partially blocked by phentolamine and totally inhibited by perphenazine or haloperidol (7). Pituitary lactotrophs seem therefore to have α- and β-adrenergic, in addition to dopaminergic, receptors. The present observation that the dopamine-induced prolactin suppression was modified by neither α- nor β-blockers suggests that, in man, dopamine acts preferentially on its own receptors and the activation of α-adrenergic receptors observed by MacLeod and Lehmeyer in the rat (7) might be ascribed to the larger amount of dopamine used or to a peculiarity of that animal species. Although our study cannot discriminate between a pituitary and a hypothalamic locus of action of dopamine in suppressing prolactin secretion, it does indicate that, if a hypothalamic site is involved, this is easily accessible by systemically administered dopamine.

This consideration might help to interpret the profound discrepancy between the consistency of prolactin inhibition and the absence of growth hormone stimulation by dopamine. A differential sensitivity of the prolactin and growth hormone secretory systems to dopaminergic agents is unlikely because they are both susceptible to small doses of apomorphine (37), whereas even larger doses of dopamine have failed to affect growth hormone levels but do suppress plasma prolactin (5, 6). The absence of growth hormone response to systemically administered dopamine is likely to depend upon two factors: (*a*) pituitary somatotrophs are insensitive to the direct action of catecholamines, including dopamine (35, 36), and (*b*) the ventromedial hypothalamic nucleus, where the signal for growth hormone secretion most likely originates (38), is not easily reachable by peripherally administered dopamine (39). This latter consideration is supported by the finding that, in man, carbidopa, a specific inhibitor of peripheral aromatic amino acid decarboxylase, elevates plasma prolactin significantly without affecting growth hormone levels (14). However, the occurrence of a growth hormone rise in some subjects during the combined administration of propranolol and dopamine would indicate that, at least in some instances, a small amount of catecholamine can cross the barrier and result in growth hormone stimulation when the system has been "sensitized" by propranolol.

The mechanism by which propranolol allows not only dopamine but also other catecholamines (40, 41) to induce growth hormone secretion is still speculative. It may exert its effect at the periphery by lowering the level of FFA, which have been shown to modulate growth hormone secretion effectively (42), or, because it easily crosses the blood-brain barrier (43), it might reduce an inhibitory central adrenergic tone or interfere with glucose metabolism in the brain (44). It is therefore impossible at this time to draw any conclusions about nonadrenergic vs. adrenergic effects of dopamine on the growth hormone secretory system.

However, it can be stated that, in man, the changes in circulating glucagon, insulin, and prolactin levels observed during systemic infusion of dopamine are not mediated through activation of adrenergic receptors. This observation should hasten a more precise definition of the mechanism(s) involved in dopamine's action on these hormonal systems. Whereas a wealth of animal and in vitro experiments support the contention that the prolactin-secreting cells are endowed with specific dopaminergic receptors, the same suggestive evidence is not yet available for pancreatic α- and β-cells. It should not be forgotten that these cells belong to the amine-precursor uptake and decarboxylation system and are therefore able to take up dopamine (45) and eventually express an intracellular effect of the catecholamine. In addition, pancreatic α- and β-cells, although responsive to *l*-dopa (31, 37), have proven insensitive to apomorphine, a specific agonist at dopamine receptors (37). The evaluation of other dopaminergic agonists and antagonists will contribute critical information on the location and characteristics of the receptors involved in dopamine's action on the endocrine pancreas.

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