Is Aldosterone Secretion under Dopaminergic Control?

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ALTHOUGH angiotensin, potassium, sodium, and adrenocorticotropic hormone are generally acknowledged as major direct influences on aldosterone secretion, there is a strong case for the existence of other factors which affect aldosterone secretion and which may play physiological roles (see Coghlan et al., 1979, for review). The plasma aldosterone response to metoclopramide (a dopamine antagonist) initially reported by Norbiato et al. (1977) is independent of known aldosterone-controlling factors and suggests the existence of a novel aldosterone-regulating mechanism. The proposition that aldosterone production may be subject to dopaminergic inhibition was originally suggested by Eldwards et al. (1975) and received support from the in vitro studies of McKenna et al. (1979). Recently, Carey et al. (1979; 1980) and Noth et al. (1980) have postulated aldosterone secretion to be under maximal tonic dopaminergic inhibition in normal man. This postulate rests upon two observations—that, although metoclopramide causes plasma aldosterone to rise 2- to 3-fold (Norbiato et al., 1977; Brown et al., 1979a; Carey et al., 1979, 1980; Bevilacqua et al., 1980; Coghlan et al., 1980; Edwards et al., 1980; Noth et al., 1980), neither dopamine nor bromocriptine (a dopamine agonist) modify basal plasma aldosterone (Carey et al., 1979, 1980; Noth et al., 1980).

The present review will survey recent studies of the effects on aldosterone of dopamine agonists and antagonists, including bromocriptine and metoclopramide, and of drugs modifying dopamine metabolism. The results of these studies will be related to the hypothesis of a physiological role for dopamine in aldosterone control. Finally, an assessment of the relative merits of the case for and against a role for dopamine in aldosterone control will be presented.

Metoclopramide and Aldosterone

Although an initial study reported metoclopramide, 5 mg, iv, to be without effect on plasma aldosterone (Ogihara et al., 1977), all subsequent studies have shown an increase in plasma aldosterone in response to metoclopramide administration. An intravenous bolus of 10 mg metoclopramide produces a rapid 2- to 3-fold increase in plasma aldosterone, which reaches a peak between 2 and 10 minutes and returns to basal levels over the next 1-3 hours in both man (Norbiato et al., 1977; Brown et al., 1979a; Carey et al., 1979, 1980; Bevilacqua et al., 1980; Edwards et al., 1980; Noth et al., 1980) and sheep (Coghlan et al., 1980). In contrast, oral metoclopramide (10 mg) produced a rise in plasma aldosterone in only two of five subjects (Noth et al., 1980). The increase in plasma aldosterone is accompanied by a parallel increase in urinary excretion of the acid-labile conjugate of aldosterone (Carey et al., 1979, 1980; Noth et al., 1980).

The effect of metoclopramide upon aldosterone secretion appears to be independent of known aldosterone-regulating mechanisms. The plasma aldosterone response to metoclopramide is not associated with any change in blood pressure, pulse rate, or plasma levels of sodium, renin activity, cortisol, or fluorogenic steroids (Norbiato et al., 1977; Carey et al., 1979, 1980; Brown et al., 1979a; Bevilacqua et al., 1980; Coghlan et al., 1980; Edwards et al., 1980; Noth et al., 1980). Bevilacqua et al. (1980) reported that metoclopramide causes a significant decrease in serum potassium (~0.3 mEq)
10 and 20 minutes post iv injection, an effect not found in the other studies cited above. Metoclopramide has been reported to increase plasma aldosterone in patients with primary aldosteronism due to bilateral adrenal hyperplasia or adenomata (Norbiao et al., 1977; Brown et al., 1979b) and also in three of six anephric patients (Pratt et al., 1979). Supplemental dietary sodium (155 mmol daily for 2 days) did not appear to modify the plasma aldosterone response to metoclopramide (Brown et al., 1979a).

A role for the pituitary in the effect of metoclopramide on aldosterone secretion has not been formally excluded. Evidence against an involvement of the pituitary includes the following: (1) Pratt et al. (1979) reported a 3- to 4-fold increase in plasma aldosterone in response to metoclopramide in five hypopituitary patients in whom plasma prolactin remained undetectable or unchanged by metoclopramide. (2) Dexamethasone administration does not prevent the plasma aldosterone response to metoclopramide administration (Norbiao et al., 1977; Brown et al., 1979a). Norbiao et al. (1977) claimed that metoclopramide elevated plasma aldosterone in two hypophysectomized patients, although the plasma cortisol levels reported for these patients suggest incomplete hypophysectomy.

**Sulpiride and Aldosterone**

Sulpiride is a substituted benzamide and is thus structurally related to metoclopramide. Many of the properties of sulpiride, including dopamine antagonism, are similar to those of metoclopramide (Trabucchi et al., 1975; Roufogalis et al., 1976; Elliott et al., 1977; Jenner and Marsden, 1979; Meltzer et al. 1977; Niemegeers and Janssen, 1979). In contrast to metoclopramide, however, sulpiride possesses antipsychotic effects similar in potency to chlorpromazine (Bratfos and Haug, 1979).

Mori et al. (1980) have recently reported the failure of sulpiride (50 mg, im) to increase plasma aldosterone in normal subjects on either a normal, low sodium, or high sodium diet. In contrast, Costa et al. (1980) reported that sulpiride (100 mg) produced a significant increase in plasma aldosterone within 5 minutes of intramuscular injection and a maximal (3-fold) increase at 30 minutes. Plasma prolactin showed a 6-fold increase; however, there were no changes in plasma renin activity, cortisol, or potassium concentration. In addition, Costa et al. (1980) have reported sulpiride to be a direct stimulus of aldosterone production by superfused bovine adrenal cortex. This stimulus was associated with an increase in cyclic AMP content of the tissue, but with no change in cortisol production.

**Chlorpromazine and Aldosterone**

Chlorpromazine possesses both central and peripheral dopamine antagonist activity, in addition to a adrenergic receptor blocking activity (Brotzu, 1970; Caron et al., 1978). Intravenous administration of chlorpromazine (10 and 25 mg) to schizophrenic patients does not cause the abrupt increase in plasma aldosterone which occurs with metoclopramide. There is, in contrast, a delayed rise in plasma aldosterone, significant at 60 minutes; this aldosterone elevation is preceded by a rise in plasma renin activity (Robertson and Michelakis, 1975). The difference in aldosterone response to chlorpromazine and metoclopramide does not necessarily exclude a dopaminergic mechanism for metoclopramide, in that it may reflect differences in the actions of these substances on different dopamine mechanisms. For example, these two drugs have been shown to differ markedly in antipsychotic effect and in actions on dopamine-sensitive adenylate cyclase (Borenstein and Bles, 1965; Roufogalis et al., 1976; Meltzer et al., 1979).

**Bromocriptine and Aldosterone**

In contrast to the general agreement between different laboratories regarding the plasma aldosterone response to metoclopramide, there are a number of contradictory studies on the effect of oral bromocriptine administration on plasma aldosterone.

There is general agreement that bromocriptine is without effect on basal supine plasma aldosterone levels in normal man (Birkhäuser et al., 1979; Del Pozo et al., 1977; Carey et al., 1979, 1980; Whitfield et al., 1980) and in patients with primary aldosteronism due to bilateral adrenal hyperplasia or aldosterone-producing adenomata (Mantero et al., 1977). Birkhäuser et al. (1979) and Del Pozo et al. (1977) have reported bromocriptine to be without effect on the plasma aldosterone response to upright posture in normal man; in contrast, Whitfield et al. (1980) reported bromocriptine to completely inhibit the plasma aldosterone response to upright posture. Furthermore, Mantero et al. (1977) reported that bromocriptine impaired the plasma aldosterone response to upright posture in seven subjects with primary aldosteronism due to bilateral adrenal hyperplasia, but did not affect the response in three patients with aldosterone-producing adenomata.

Birkhäuser et al. (1979) reported bromocriptine to partially inhibit the plasma aldosterone response to adrenocorticotrophic hormone, but this was not confirmed by Whitfield et al. (1980). However, both Birkhäuser et al. (1979) and Whitfield et al. (1980) have reported bromocriptine to inhibit the plasma aldosterone response to angiotensin infusion. In contrast, Carey et al. (1979) found bromocriptine to be without effect on the plasma aldosterone response to graded angiotensin infusion. Furthermore, bromocriptine, at a dose which suppressed basal serum prolactin levels and completely inhibited the prolactin response to metoclopramide, had no effect on the plasma aldosterone response to metoclopramide (Carey et al., 1980).

Edwards et al. (1975) reported bromocriptine to inhibit the plasma aldosterone response to intra-
venous frusemide. This report, however, is difficult to interpret given the small number of subjects studied, the apparent rise in plasma aldosterone after an acute dose of bromocriptine, and the erratic changes in plasma renin activity. Other studies have reported bromocriptine to be without effect on the plasma aldosterone response to low sodium diet (Semple and Mason, 1978), the diurnal rhythm of plasma aldosterone (Uberti et al., 1979), or urinary aldosterone excretion (Birkhäuser et al., 1979). Similarly, bromocriptine did not affect the rise in plasma aldosterone occurring between dialyses in patients with renal failure (Øigaard et al., 1977), nor plasma aldosterone levels in acromegalic patients, despite a significant fall in plasma renin activity (Nilsson and Hökfelt, 1978).

At the present time, therefore, there is some confusion regarding the effect of bromocriptine on the plasma aldosterone response to various stimuli. Further study will be required to delineate the extent to which differences in methodology may have contributed to the different results reported by different laboratories.

Bromocriptine, however, is neither exclusively dopaminergic, possessing a dopamine receptor antagonist activity (Gibson and Samini, 1978), nor is it a pure dopamine agonist. It is, for example, without effect on the vascular dopamine receptor (Goldberg et al., 1978). In addition, bromocriptine not only fails to stimulate striatal dopamine-sensitive adenylate cyclase, but has been shown to antagonize the stimulatory effects of dopamine (Trabucchi et al., 1976; Markstein et al., 1978). Bromocriptine may also inhibit some dopaminergic mechanisms by stimulation of presynaptic inhibitory dopamine receptors on dopaminergic nerve terminals (Di Chiara et al., 1978). It is important to note that ergot derivatives such as bromocriptine are at least an order of magnitude less potent than dopamine itself in inhibiting prolactin secretion (Caron et al., 1978). Thus, whereas suppression of plasma prolactin is a valuable positive control in the study of dopamine agonist properties of bromocriptine, it may be a quite inappropriate index of dopaminergic mechanisms in which bromocriptine has an agonist potency equal to or less than that of dopamine itself.

Given that bromocriptine (1) has effects on systems other than dopaminergic, (2) may be agonist, antagonist, or inactive, depending on the dopaminergic system studied, it seems unwise to extrapolate from an effect—or lack of effect—of bromocriptine on aldosterone secretion to precise roles for dopamine in aldosterone control.

Parkinson’s Disease, L-Dopa, and Aldosterone

Parkinson’s disease provides a unique though restricted model to study the effects of disordered dopamine metabolism. Both idiopathic and postencephalitic Parkinson’s disease are characterized by a marked reduction in striatal dopamine (Hornykiewicz, 1966). That this disorder is not confined to the central nervous system is suggested by reports of an associated significant reduction in urinary dopamine excretion (Barbeau et al., 1961, 1969). However, patients with Parkinson’s disease show no evidence of aldosterone “escaping” from the postulated tonic dopaminergic inhibitory control. Barbeau et al. (1969), in a study of five representative Parkinsonian patients, found plasma aldosterone to be normal in four patients and elevated in one. Aldosterone secretion rates were in the lower limit of the normal range.

The effects of administered L-dopa are contingent upon decarboxylation to dopamine in all situations studied (Kopin, 1973; Watanabe et al., 1971; Blair et al., 1977). L-Dopa administration results in elevated blood, tissue, and urinary dopamine levels (Romero et al., 1973; Tyce et al., 1974; Louis et al., 1974). Parkinsonian patients on chronic L-dopa therapy have normal plasma aldosterone levels and normal urinary aldosterone excretion which show normal responses to a low sodium diet or frusemide administration (Sullivan et al., 1973; Katz and Hoehn, 1977). A sequential study of four Parkinsonian patients during the introduction of L-dopa therapy showed no significant alteration in plasma aldosterone or urinary aldosterone excretion (Katz and Hoehn, 1977).

Dopamine and Aldosterone

Both Carey et al. (1980) and Noth et al. (1980) have shown intravenous dopamine to be without effect on plasma aldosterone in normal man. In contrast, both groups reported that dopamine infusion inhibited the plasma aldosterone response to metoclopramide.

McKenna et al. (1979) have reported dopamine to be without effect in vitro on basal aldosterone production by bovine adrenal glomerulosa cells, but to inhibit angiotensin stimulated aldosterone production. Dopamine concentrations greater than 10 nM were required to produce significant inhibition and 10 μM caused submaximal (50%) inhibition.

Idiopathic Edema, L-Dopa, Metoclopramide, and Aldosterone

The syndrome of idiopathic edema is characterized by high plasma renin and aldosterone, sodium retention, low urinary dopamine, and a blunted urinary dopamine and sodium response to frusemide (Kuchel et al., 1977). Norbiano et al. (1979) have reported that the treatment of patients with idiopathic edema with the combination of L-dopa and carbidopa produced an improvement in both clinical and biochemical abnormalities. They suggested that these results were consistent with “a decrease in dopaminergic activity in the glomerular zone of the adrenals,” with subsequent release of aldosterone production from dopaminergic inhibition in idiopathic edema. However, patients with idio-
pathic edema showed elevations in both renin and aldosterone, and parallel decreases with L-dopa/ carbidopa treatment. Thus the effects of the treat-
ment on plasma aldosterone may be secondary to cen-
tral dopamine mechanisms which inhibit renin release (Blair et al., 1977). More importantly, pa-
tients with idiopathic edema demonstrated a much
greater absolute increase in plasma aldosterone in
response to metoclopramide (10 mg, iv) compared
to control subjects; the percentage increase (an
approximate doubling) was similar to that seen in
control subjects. This is the exact opposite of what
would be expected if the elevated plasma aldoster-
one in patients with idiopathic edema were second-
ary to a decrease in dopaminergic inhibition of
aldosterone secretion and the effects of meto-
clopramide due to its dopamine antagonist effects.

Methyldopa and Aldosterone

Methyldopa inhibits tyrosine hydroxylase (Ur-
etský et al., 1975) and dopa decarboxylase (Gold-
berg et al., 1960); in addition, the drug causes a
reduction in the tissue content of dopa decarbox-
ylase (Culvenor and Jarrott, 1979), with a resulting
marked fall in tissue levels of free dopamine (Con-
way et al., 1978). Side effects of methyldopa include
hyperprolactinemia, extrapyramidal signs, and par-
klinism (Frohlich, 1980). Evidence that the in-
crease in plasma prolactin produced by methyldopa
due to a decrease in dopaminergic inhibition of
aldosterone secretion is due to a reduction in dopaminergic inhibition of the lactotropes rather than a direct effect of methyldopa or its metabolites, has been provided by Wiggins et al. (1980).

These anti-dopaminergic effects of methyldopa,
h owever, are not associated with an increase in
aldosterone production. Cannon et al. (1962) found
no change in aldosterone secretion rate measured
3-6 days after institution of methyldopa therapy.
These workers also found no significant effects of
methyldopa therapy on sodium or potassium bal-
cance during metabolic balance studies. Other work-
ers have reported either no change or a fall in
plasma aldosterone or urinary aldosterone excretion
during methyldopa therapy which may be associ-
ated with a fall in plasma renin activity (Safar et
al., 1975; Gavras et al., 1977; Alcocer et al., 1978).
Thus, studies of the effect of methyldopa on aldo-
sterone, though limited, provide no support for the
hypothesis that aldosterone is normally subject to
dopaminergic inhibition.

Discussion

The stimulation of aldosterone production by the
related compounds, metoclopramide and sulpiride,
are important observations providing new insight
into aldosterone control. Since the bulk of current
evidence relates to metoclopramide, the present
discussion will focus on the question of the mecha-
nism by which metoclopramide increases aldoster-
one production.

In the absence of a direct effect of dopamine
agonists upon plasma aldosterone in many studies,
and the failure of chlorpromazine and methyldopa
to increase aldosterone production, the case for a
role of dopamine in aldosterone control rests mainly
upon the dopamine antagonist properties of meto-
clopramide. The failure of dopamine agonists to
affect plasma aldosterone in vivo led Carey et al.
(1979, 1980) and Noth et al. (1980) to postulate that
aldosterone secretion is under maximum tonic do-
paminergic inhibition. However, dopamine agonists
and metoclopramide have multiple actions, both
dopamine related and independent of dopaminergic
mechanisms, and current evidence does not permit
a definitive statement on the role of dopamine in
aldosterone control.

Dopamine Agonists and the Dopamine
Hypothesis

If aldosterone secretion is subject to a dopami-
nergic inhibitory mechanism, an important ques-
tion is the site of this postulated mechanism. In
terms of an adrenal site for this mechanism, there
is no information on the concentration of dopamine
in the zona glomerulosa. Catecholamine fluores-
cence histochemical studies of both normal and transplanted sheep adrenal cortex show sparse post-
ganglionic amnergic innervation which enters the
gland with the supplying arteries (Wright et al.,
1972; Robinson et al., 1977). It is not known if these
are dopaminergic neurons, such as have been de-
scribed associated with the juxtaglomerular vessels
of the renal cortex, the arteriovenous anastomoses
of the paw pads in the dog, the retina, glomus
caroticum, and within sympathetic ganglia (Unger-
stedt, 1978; Bell and Lang, 1979). Dopamine nor-
maally constitutes 1-2% of total catecholamine con-
tent of the adrenal; the major part, if not all, of this
dopamine is located within the adrenal medullary
cells (see Almgren et al., 1979, for review). Whereas
the adrenal medulla represents a rich source of
dopamine, it is unlikely that the zona glomerulosa
is directly exposed to dopamine from the adrenal
medulla, in view of the direction of blood flow from
the capsule to the medulla and the high rate of
adrenal blood flow (Wright, 1963).

Kvetnánský et al. (1979) have recently reported
that adrenal medullectomy produced only a 50% re-
duction in adrenal dopamine content. This rather
surprising result may, however, have a methodolog-
ic basis, since the levels of adrenal dopamine mea-
sured were greater than 10-fold higher than esti-
mates from other laboratories (Snider and Carlson,
1972; Romero et al., 1973; Almgren et al., 1979).

Circulating levels of free dopamine are very low,
less than 0.3 nM (see Da Prada and Zuercher, 1979,
for review). Higher reported values for plasma do-
pamine measured by earlier methodology may rep-
resent hydrolysis of conjugated dopamine (Gold-
In contrast to epinephrine and norepinephrine, the origin of plasma dopamine remains at present relatively obscure. Plasma dopamine levels remain relatively constant; they do not reflect sympathetic neural tone and remain unaltered by adrenalectomy (Da Prada and Zuercher, 1979).

Plasma dopamine is therefore unlikely to have a humoral function. Micromolar concentrations of dopamine are required to produce relaxation of isolated mesenteric vasculature (Brodde and Scheimuth, 1979), renal vasodilation (Imbs et al., 1979), or to activate dopamine-sensitive adenylate cyclase in the renal artery (Gilbert et al., 1979) and brain (Sano et al., 1979). Dissociation constants ($K_d$) for dopamine receptors in the pituitary (36 nM, Caron et al., 1978; 65 nM, Cronin et al., 1978) and sympathetic presynaptic receptors of the rabbit ear artery (37 nM, Steinsland and Hieble, 1978) are one hundred times the concentration of peripheral plasma dopamine. It is, however, possible that plasma dopamine may affect some very high affinity receptors such as those described in rat brain ($K_d = 2-3$ nM (List et al., 1980); $K_d = 7$ nM (Burt et al., 1975)), if such receptors exist outside the blood-brain barrier. The present proposal that peripheral plasma dopamine lacks a humoral function is analogous to the lack of a humoral function described for basal levels of plasma norepinephrine (Silverberg et al., 1978).

The vascular content of dopamine is minimal (Head and Berkowitz, 1979; Bell and Lang, 1979); this argues against a prominent role for endogenous dopamine in directly modulating cardiovascular responses, since most of the dopamine in adrenergic neurons is converted to norepinephrine (Hope et al., 1978). This conclusion is supported by the observation that metoclopramide, 20 mg by intravenous bolus injection, is without detectable hemodynamic effect in patients undergoing cardiac catheterization (Thorburn and Sowton, 1973), since metoclopramide blocks both vascular and post-ganglionic presynaptic dopamine receptors (Day and Blower, 1975; Hope et al., 1978; Brodde and Scheimuth, 1979).

The above data suggest that the zona glomerulosa is unlikely to be exposed to significant amounts of free dopamine. However, in contrast to the very low levels of free dopamine normally present in plasma, both conjugated dopamine and dopa are present in relatively high amounts in normal human plasma (Buu and Kuchel, 1977; Johnson et al., 1978; Da Prada and Zuercher, 1979). Both conjugated dopamine and dopa are potential sources of free dopamine and both have been implicated in peripheral non-neuronal dopamine processes (Louis and Sampson, 1974; Baines and Chan, 1979; Unger et al., 1979).

The report by McKenna et al. (1979) that dopamine inhibits angiotensin-stimulated aldosterone production in vitro is inconsistent with the lack of effect of dopamine infusion in vivo on basal plasma aldosterone (Carey et al., 1980; Noth et al., 1980), since basal aldosterone production is partially dependent upon endogenous angiotensin stimulation, as evidenced by the plasma aldosterone response to converting enzyme inhibition (Bravo and Tarazi, 1979; Morganti et al., 1980). Similarly, the finding that 10 μM dopamine caused submaximal (50%) inhibition of angiotensin-stimulated aldosterone production in vitro (McKenna et al., 1979) is inconsistent with the hypothesis that aldosterone is subject to tonic maximal dopaminergic inhibition, at least at the level of the zona glomerulosa cell. These findings are, in addition, difficult to reconcile with the in vivo studies by Carey et al. (1979), who found no enhancement by metoclopramide of the aldosterone response to angiotensin infusion.

A series of studies arguing against an adrenal dopaminergic mechanism controlling aldosterone production has been carried out in sheep with adrenal autotransplants. Systemic administration of metoclopramide increases aldosterone production in such sheep; an equivalent dose of metoclopramide, on a blood flow basis, injected into the adrenal artery, is without effect on aldosterone secretion (J.P. Coghlan, personal communication).

**Metoclopramide and the Dopamine Hypothesis**

Metoclopramide belongs to a new class of compounds known as substituted benzamides, and neither the peripheral nor central mechanism of action of these compounds is clearly understood (see Jenner and Marsden, 1979, for review). Whereas metoclopramide has well-established dopamine antagonist effects (Day and Blower, 1975; Ahtee, 1975; Peringer et al., 1976; Yeo et al., 1979), many dopamine mechanisms are unaffected by metoclopramide and some effects of metoclopramide may be unrelated to dopaminergic mechanisms.

Both central and peripheral dopaminergic mechanisms are complex and incompletely understood. Current knowledge of dopamine receptors emphasizes a diversity in receptor topography, effects mediated, and specificity for agonists and antagonists (for review see Goldberg et al., 1978; Kebabian and Calne, 1979). Recently, Kebabian and Calne (1979) have proposed a classification of dopamine receptors based upon linkage of the receptors to adenylate cyclase (D1 receptors) or no cyclase linkage (D2 receptors). Metoclopramide has been proposed as a specific antagonist of D2 receptors (Kebabian and Calne, 1979). Central dopaminergic nerve terminals possess presynaptic dopamine receptors which, when stimulated, serve to decrease dopamine release from the terminal (Carlsson, 1977; Aghajanian and Bunney, 1977). Metoclopramide is
able to block these presynaptic receptors in some situations (Kehr and Debus, 1979), though not others (Kebabian and Kebabian, 1978), and may thus enhance some dopaminergic mechanisms by inhibiting negative feedback of dopamine release.

Some of the effects of metoclopramide appear likely to be due to antiserotonin properties (Fozard and Mobarak Ali, 1978; Niemeegers and Janssen, 1979). In addition, metoclopramide has marked effects on gastroesophageal tone and motility; there is debate as to whether these effects are due to dopaminergic antagonism (Hay, 1975; Valenzuela, 1976; Goldberg et al., 1978). Other possible "non-dopamine" actions of metoclopramide include stimulation of the release of pancreatic polypeptide (Spitz et al., 1979) and motilin (Byrnes et al., 1980).

The site of action and the mechanism by which metoclopramide stimulates aldosterone secretion have been the subject of a number of investigations. Evidence against a direct effect on the zona glomerulosa cell is the finding that metoclopramide did not affect aldosterone production by bovine zona glomerulosa cells in vitro (Brown et al., 1979a). This finding is supported by the failure of metoclopramide to increase aldosterone production when injected into the adrenal artery of sheep with adrenal autotransplants (cited above). In contrast, Costa et al. (1980) have reported sulpiride to directly stimulate aldosterone production by superfused bovine adrenal cortex, and Edwards et al. (1980) have reported metoclopramide to directly stimulate aldosterone production by superfused rat zona glomerulosa cells. The significance of these two superfusion studies requires further investigation. In particular, there are several questions regarding the nature of the aldosterone response of superfused zona glomerulosa cells to exogenous agonists. The results of Edwards et al. (1980) show that the aldosterone response to metoclopramide does not conform to a classical dose-response curve. In addition, these workers have also reported bromocriptine, but not dopamine, to directly stimulate aldosterone production by superfused rat zona glomerulosa cells (Boscaro et al., 1979), an observation at variance with studies of bromocriptine in vivo discussed above.

If these two superfusion studies on metoclopramide and sulpiride do reflect the mechanism by which these agents stimulate aldosterone production in vivo, then they suggest that metoclopramide and sulpiride act as true agonists to stimulate aldosterone production. Such an action in vivo would then be independent of any putative endogenous dopaminergic mechanism, given that dopamine appears to be without effect on basal or angiotensin-stimulated aldosterone production (Edwards et al., 1980). Given that dopamine was an effective inhibitor of the aldosterone response to metoclopramide in these studies (Edwards et al., 1980), the most plausible hypothesis for dopaminergic modulation of aldosterone secretion in vivo, based on these superfusion studies, would appear to require the proposal of an endogenous "metoclopramide-like" stimulatory factor.

There is conflicting evidence as to the involvement of a dopaminergic mechanism in the stimulation of aldosterone by metoclopramide in vivo. The failure of bromocriptine to reduce the plasma aldosterone response to metoclopramide (Carey et al., 1980) may be attributed to different actions of these two compounds upon different dopaminergic mechanisms. That bromocriptine abolished the plasma prolactin response to metoclopramide without affecting the aldosterone response completely dissociates the aldosterone response from the prolactin response to metoclopramide.

Both Carey et al. (1980) and Noth et al. (1980) have reported intravenous dopamine infusions to be without effect on basal plasma aldosterone, but to inhibit the plasma aldosterone response to metoclopramide. However, while these data are consistent with metoclopramide acting via a maximum tonic dopaminergic mechanism, this should be a cautious conclusion, given the wide spectrum of effects produced by dopamine. In addition to effects mediated by dopamine receptors, intravenous dopamine is also able to stimulate both a and b adrenoceptors (Goldberg, 1972; Goldberg et al., 1978). Noth et al. (1980) infused dopamine at a rate sufficient to increase systolic blood pressure by 10 mm Hg. The average rate of infusion was 3.4 μg/kg per min (range 2.5–5.0) and there was an associated increase in pulse rate. Carey et al. (1980) used two dopamine infusion rates (2 and 4 μg/kg per min). Pulse rate was not reported, but the higher infusion rate increased systolic blood pressure. The increase in pulse rate and blood pressure resulting from intravenous dopamine infusion represent a b adrenoceptor stimulation, respectively, and do not impair the pressor effect of the dopamine infusion (Carey et al., 1980; Noth et al., 1980) supports this interpretation.

A major problem in the interpretation of the effect of intravenous dopamine on the aldosterone response to metoclopramide is to decide whether the effect of dopamine was due to a specific agonist effect on dopamine receptors or a nonspecific effect, mediated by a or b adrenoceptor stimulation or by some other mechanism. In support of a nonspecific effect of dopamine is the preliminary report by Hollifield et al. (1980) describing the inhibition of the aldosterone response to angiotensin and adrenocorticotropic hormone by intravenous dopamine infusion. Hollifield et al. (1980) reported dopamine infusion to be without effect on aldosterone metabolic clearance rate in patients with primary aldosteronism. However, given that dopamine infusion increases hepatic blood flow (Angehrn et al., 1980), the effect of dopamine agonists on aldosterone metabolic clearance rate will need to be studied further in normal man. Thus, given the diverse nature of the pharmacology of both metoclopramide and do-
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metoclopramide, the blockade of the metoclopramide effect on plasma aldosterone by dopamine does not constitute an unequivocal demonstration of an endogenous physiological dopamine mechanism inhibiting aldosterone secretion.

If the metoclopramide effect on aldosterone secretion is the result of blockade of a dopaminergic mechanism inhibiting aldosterone secretion, and if such a dopaminergic mechanism plays a physiological role in aldosterone control, then one might anticipate that the effects of dopamine agonists and metoclopramide on aldosterone would vary with changes in electrolyte status. Coghlan et al. (1980) have reported that intravenous metoclopramide causes elevations in plasma aldosterone in both sodium-replete and sodium-depleted sheep. The absolute increase in plasma aldosterone was much greater in the depleted sheep; however, when expressed as percent change, the increase in plasma aldosterone was less in the depleted sheep. These data might be interpreted as suggesting a reduced dopaminergic inhibition of aldosterone secretion in the sodium-deplete state.

Data from patients with primary aldosteronism are difficult to interpret. The disorder may result from decreased dopaminergic inhibition of aldosterone secretion; the suppression by bromocriptine of the posture-induced rise in plasma aldosterone in patients with bilateral adrenal hyperplasia (Mantero et al., 1977) is consistent with this view. However, Kuchel et al. (1979) have reported increased plasma and urinary dopamine in primary aldosteronism due to bilateral adrenal hyperplasia or adenoma. The plasma aldosterone response to metoclopramide administration in patients with primary aldosteronism (Noriato et al., 1977; Brown et al., 1979b) does not suggest a reduction of a postulated dopaminergic inhibition of aldosterone secretion. Similarly, in idiopathic edema, where reduced dopaminergic inhibition of aldosterone secretion has been suggested to play a role (Noriato et al., 1979), the plasma aldosterone response to metoclopramide administration does not suggest a reduction of a dopaminergic inhibitory mechanism.

Some insight into the mechanism by which metoclopramide stimulates aldosterone secretion might be achieved by study of the interaction between metoclopramide and other aldosterone-stimulating factors. Intravenous administration of metoclopramide does not affect the absolute rise in aldosterone subsequent to angiotensin infusion (Carey et al., 1979), although the percentage response was less due to the 2-fold elevation in plasma aldosterone after prior metoclopramide administration. This result does not suggest that metoclopramide amplifies the adrenal response to angiotensin, as might be expected with the lifting of a tonic inhibitory mechanism. Rather, it may indicate that metoclopramide and angiotensin act by independent mechanisms.

Whereas the question of the mechanism of the interaction between metoclopramide and dopamine administration on plasma aldosterone remains open, there is some value in comparing the aldosterone and prolactin responses to metoclopramide and dopamine, and in speculating about the properties of the hypothetical dopaminergic mechanism controlling aldosterone. A comparison of the prolactin response with the aldosterone response to metoclopramide demonstrates a number of differences which suggest that there is a significantly greater threshold plasma metoclopramide concentration for the aldosterone response:

1. Intravenous injection of 5 mg metoclopramide was without effect on plasma aldosterone (Ogihara et al., 1977), whereas 10 mg metoclopramide causes a 2- to 3-fold increase in plasma aldosterone (Noriato et al., 1977; Carey et al., 1979; 1980; Brown et al., 1979a; Bevilacqua et al., 1980; Edwards et al., 1980; Noth et al., 1980; Coghlan et al., 1980). In contrast, 1 mg of metoclopramide, iv, causes a greater than 4-fold increase in plasma prolactin (Kitaoka et al., 1980).

2. Oral metoclopramide (10 mg) produced an increase in plasma aldosterone in only two of five subjects, in contrast to the 10-fold increase in plasma prolactin (Noth et al., 1980).

3. In the studies of Carey et al. (1980) and Noth et al. (1980), described above, upon cessation of the dopamine infusion 1 hour after intravenous injection of 10 mg metoclopramide, there was a rebound increase in plasma prolactin to levels produced by metoclopramide in the absence of dopamine infusion. In contrast, plasma aldosterone showed no response to cessation of dopamine infusion 1 hour after metoclopramide administration.

This increased threshold phenomenon demonstrated by the aldosterone response to metoclopramide is consistent with the postulated maximum tonic dopaminergic inhibition of aldosterone production. The concept of maximum tonic dopaminergic inhibition of aldosterone production implies that the aldosterone-dopamine dose-response curve normally lies far to the left of the prevailing dopamine concentration in the vicinity of the putative dopamine receptor controlling aldosterone. Thus, the high threshold concentration of metoclopramide may be required to shift the aldosterone-dopamine dose-response curve to the right by a distance sufficient to release aldosterone from dopaminergic inhibition.

Intravenous infusion of dopamine at 2 and 4 µg per min inhibited the plasma prolactin and aldosterone responses to metoclopramide by similar proportions and in a dose-related manner (Carey et al., 1980). This suggests that the putative dopamine receptor controlling aldosterone is outside the blood-brain barrier and subject to a prevailing dopamine concentration similar to that which exists in the anterior pituitary in the vicinity of the lactotropes. Plasma dopamine levels during dopamine infusion were not reported by Carey et al. (1980) or
ject to tonic dopaminergic inhibition is a reasonable hypothesis, given the current data. However, much more work is required to substantiate or disprove the hypothesis. The basis of the hypothesis is the aldosterone response to metoclopramide. Yet the site of action of metoclopramide in vivo—whether adrenal or extra-adrenal—will require further investigation before the various contradictory in vitro studies can be adequately interpreted. To help define whether the aldosterone response to metoclopramide in vivo is due to its dopaminergic antagonist properties, it will be necessary to study both the magnitude and time course of the aldosterone response to a range of doses of metoclopramide, preferably with infusion of metoclopramide and monitoring of plasma metoclopramide levels. Further study of the effect of other dopamine antagonists and dopa decarboxylase inhibitors on aldosterone production is indicated. If other dopamine antagonists do not stimulate aldosterone production, it will be important to determine whether any of the "aldosterone ineffective" dopamine antagonists can reverse the inhibition by dopamine infusion, of the metoclopramide-stimulated aldosterone production.

It would appear that alternatives to a tonic maximal dopaminergic inhibition of aldosterone should be considered. Possible alternative mechanisms by which metoclopramide may stimulate aldosterone secretion include (1) an acute interaction with a specific central or peripheral dopaminergic mechanism which is normally unrelated to aldosterone control, with adventitious stimulation of aldosterone secretion; (2) mimicking the action of an unknown endogenous agonist, in a system in which dopamine is antagonist, analogous to the postulated interaction between opiates and dopamine on prolactin secretion by the lactotrope (Enjalbert et al., 1979); (3) that the action of metoclopramide on aldosterone secretion is totally unrelated to its dopaminergic antagonist effects and the inhibition by dopamine of metoclopramide stimulation of aldosterone is due to a "nonspecific" effect of dopamine infusion.

In conclusion, the case for a role for dopamine in aldosterone control is far from proven and rests largely on the aldosterone response to metoclopramide administration. The mechanism by which metoclopramide stimulates aldosterone secretion remains to be defined, and further work is necessary to determine whether or not this metoclopramide effect is via blockade of a maximum tonic dopaminergic inhibition of aldosterone production.

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