Dopaminergic regulation of aldosterone secretion: how credible?

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It is generally acknowledged that the renin-angiotensin system is of prime importance in the hierarchy of factors regulating aldosterone secretion [1-4]. Potassium and adrenocorticotropic hormone (ACTH) also influence aldosterone secretion [1-4] and sodium may have a direct effect on aldosterone release independent of the renin-angiotensin system [2, 5, 6], at least in some species. From time to time it has been suggested that there may be other stimuli for aldosterone secretion [7, 8]. Serotonin [2, 9, 10] stimulates aldosterone secretion in vitro. Its physiological role, if any, is unclear. The role of prostaglandins is controversial. New aldosterone-stimulating factors distinct from ACTH or angiotensins have now been reported [11, 12]. Their precise nature still eludes complete characterization. Some of the members of the ACTH family, such as β-lipotropin, α-MSH, β-MSH and γ-MSH, also may conceivably be involved in the normal [13-17] or abnormal [18, 19] regulation of aldosterone secretion.

All of these factors have been stimulatory in nature, but in 1979 an inhibitory control of aldosterone secretion through a dopaminergic mechanism was suggested [20]. The concept had emerged as a result of a number of observations to be discussed in the succeeding section. The idea of a dopaminergic control over aldosterone secretion is of interest because a physiological role for dopamine in renal sodium excretion has been advocated [21-23]. An inhibitory effect of dopamine on aldosterone secretion, if substantiated, would be complementary to this action of dopamine on the renal handling of sodium. In this brief review I wish to critically examine the basis of the proposed concept of dopaminergic regulation of aldosterone secretion.

A series of studies by various investigators directed our attention to a possible dopaminergic influence on aldosterone secretion. Edwards et al. [24] reported that the frusemide-induced rise in plasma aldosterone concentration was blunted by prior treatment with bromocriptine, a dopamine agonist, and such an attenuation response could not be explained satisfactorily by a consistent alteration in the plasma renin response. Norbiato and his colleagues [25] observed that metoclopramide, a dopamine antagonist, increased plasma aldosterone concentration in the normal human without a concomitant increase in plasma renin activity or plasma cortisol concentration. This aldosterone-stimulating effect of metoclopramide in normal subjects is quite prompt and short-lived. Since then such an effect of metoclopramide has been confirmed in the human by a number of investigators [12, 20, 26-31]. This effect has been shown to be due to increased aldosterone secretion and not due to a change in the metabolic clearance of aldosterone [31]. A dopaminergic mechanism for the fluctuation of plasma aldosterone levels in primary aldosteronism has been suggested by Kuchel et al. [32]. Metoclopramide also evokes increased aldosterone secretion in the patients with primary aldosteronism caused by an adrenal adenoma or bilateral adrenal hyperplasia, again without any apparent involvement of known factors [29, 33-36]. Curiously, in the dexamethasone pre-treated patients with glucocorticoid-suppressible aldosteronism metoclopramide fails to elicit a
plasma aldosterone response [36]. The reason for this effect is not at present entirely clear. In various animal species reports of the effects of metoclopramide on aldosterone secretion have been variable of conflicting [37-45; G. Aguilera, unpublished observations].

Most studies [20, 27, 46-50] have failed to show any effect of dopamine or bromocriptine, a dopamine agonist, on the basal plasma aldosterone concentration in the normal human. Such a finding has been interpreted by Carey et al. [20] to construe that endogenous dopaminergic inhibition of aldosterone secretion normally is maximal and hence no further inhibitory effect of dopaminergic agent is demonstrable. Conflicting effects of dopamine or bromocriptine on stimulated aldosterone secretion in the normal human have been reported [20, 48-50]. Limited studies in the patients with primary aldosteronism showed the results of bromocriptine treatment on the basal or stimulated plasma aldosterone concentration also to be variable [34, 48, 51, 52]. The relevance of these findings to the physiology or pathophysiology of aldosterone secretion is unclear.

The basis of the action of metoclopramide in eliciting the plasma aldosterone response has assumed considerable importance since in most studies no apparent participation of any of the known physiological stimuli could be demonstrated. In view of such findings and since metoclopramide is a known dopamine antagonist, its aldosterone-stimulating effect in such a setting has lent credence to the postulate of a dopaminergic mechanism or that dopaminergic mechanism plays a physiological role in the regulation of aldosterone secretion.

More importantly, with regard to the postulated dopaminergic regulation of aldosterone secretion there are several crucial issues. If a dopaminergic mechanism is involved in the regulation of aldosterone secretion how does it operate on the adrenal cortex? Although dopamine is present in the circulating blood in sufficient quantities most of it is conjugated as sulphate or glucuronide [59]. The amount of free dopamine in the normal human peripheral blood is undetectable by present techniques [60] and may be too little to exert the necessary biological effect. Unless dopamine conjugates themselves are able to produce a biological effect in the adrenal or can be deconjugated within the adrenal it is unlikely that the circulating dopamine could participate in the regulation of aldosterone secretion. Dopamine has been claimed to be present in the adrenal cortex in the rat and a substantial amount remained in the cortex after adrenal medullectomy [61]. The source of this adrenocortical dopamine is unknown. The dopamine content of human adrenal cortex and the state in which it is present is probably not known. Adrenal medulla is a rich source of dopamine but it is unclear if the latter can be transported to the adrenal cortex from there. The available evidence points to a blood flow in the adrenal portal circulation from the cortex to the medulla rather than from the medulla to the cortex [62]. Unless a retrograde blood flow could occur intermittently the adrenal medulla probably is not the source of dopamine in the adrenal cortex. Kidney could be another source of dopamine which is thought to be involved in the regulation of urinary sodium excretion [21-23]. Vascular connections between the kidney and the adrenal may be present [63]. However, if a dopaminergic mechanism is involved locally in the adrenal steroid secretion then a neurogenic source of dopamine may be the most plausible suggestion. We know very little about the nature and the extent of innervation of the adrenal cortex, especially in man. Nerve terminals have been observed within the adrenal cortex of various species in close proximity to the cells [64-67] and it has been reported that there may be greater number of nerve endings in the subcapsular region of the adrenal cortex than in the rest of the cortex [65]. The nature of the nerves with regard to their neurotransmitters is far from clear. The innerva-
tion of the adrenal cortex actually may be cholinergic in nature [68] as it is probably in the adrenal medulla [64, 69]. Therefore, the issue whether a dopaminergic mechanism is able to exert an effect on the adrenal zona glomerulosa under physiological conditions remains clouded at best.

In such a context the site of action of metoclopramide in eliciting the aldosterone response assumes even greater interest. Pratt et al. [28] observed that metoclopramide stimulated aldosterone secretion in the patients with hypopituitarism as well as in anephric subjects, further suggesting a possible direct action of the metoclopramide on the adrenal. Although this evidence makes pituitary participation unlikely it does not entirely exclude such a possibility since a complete absence of any pituitary tissue has not been proven in the patients with hypopituitarism. Plasma prolactin and cortisol levels, however, remained unchanged in most patients. Bevilacqua et al. [70] suggested that possibly transcellular shift of potassium in the adrenal induced by metoclopramide could account for its aldosterone-stimulating effect. In several recent studies in various animal species a direct aldosterone-stimulating effect of metoclopramide on the adrenal or adrenal cells could not be demonstrated [40, 42–44]. Lauer et al. [71] reported that metoclopramide actually inhibited aldosterone secretion from rat adrenal zona glomerulosa cells. These findings have further raised questions about the site of action of metoclopramide and tend to discount the possibility of the adrenal itself being the locus of its action. However, the results of studies in vitro should be interpreted cautiously. One has to be certain that the dopamine receptors are not destroyed during the cell preparations and dopamine is available in the adrenal cells to be displaced by metoclopramide. The binding of dopamine or other agonists to the prepared cells must be demonstrated before any firm conclusion can be drawn about the lack of direct effect of metoclopramide on the adrenal.

Since a direct effect of metoclopramide on aldosterone secretion is becoming increasingly tenuous from the results of recent studies, and for reasons discussed in the preceding section, the possibility that metoclopramide may produce its anti-dopaminergic effect on aldosterone secretion by releasing another factor into the circulation has to be entertained. Several factors could be considered for such a role. It has now been shown that ACTH is processed in the pituitary as well as in the brain as a pro-opiomelanocortin precursor. The latter is cleaved to form ACTH and several other peptides [72–74]. Depending on the anatomical site, different peptides are produced [74]. For example, in the rat and in the fetal stage in man α-MSH is produced by the intermediate lobe of the pituitary [75]. In man this lobe is said to involute after birth and α-MSH is not detectable in blood in adult human [76]. ACTH and β-lipotropin are principally produced in the anterior lobe of the pituitary. The processing of the messenger RNA for ACTH in the pituitary and the hypothalamus has been shown to be regulated by glucocorticoids as well as other non-glucocorticoid factors [77], including a dopaminergic mechanism [78]. They may be independent of each other. Whether such differential processing occurs in the human remains to be established. There are other suggestions that a dopaminergic mechanism may participate in the regulation of ACTH secretion [79]. However, if metoclopramide-induced increase in aldosterone secretion were mediated by the release of ACTH then cortisol secretion should also have increased. Available data suggest that cortisol secretion is unaffected by metoclopramide, especially when metoclopramide evokes aldosterone response in subjects pretreated with dexamethasone. Therefore, such a hypothetical factor has to be something other than normal ACTH. It has been shown that β-lipotropin, α-MSH and β-MSH and possibly β-endorphin can stimulate aldosterone secretion either in vivo or in vitro [13, 16–17]. Pro-γ-MSH has been reported to potentiate the aldosterone-stimulating effect of ACTH [14, 15]. Theoretically, any of these peptides could be involved in the metoclopramide effect. If metoclopramide produces its effect by an extra-adrenal mechanism it is conceivable that an aldosterone-stimulating factor, possibly of the ACTH family, which is tonically inhibited by a dopaminergic mechanism is released by metoclopramide, causing increased aldosterone secretion in normal subjects and in patients with primary aldosteronism. This factor may or may not have any physiological role in aldosterone secretion and may be lacking in glucocorticoid-suppressible aldosteronism. However, the physiological roles of none of the pro-opiomelanocortin-derived peptides other than ACTH in the stimulation of aldosterone secretion have been demonstrated as yet. Neither α-MSH nor β-MSH is thought to be present in human blood normally and the potential ability of normally circulating β-lipotropin concentration to stimulate aldosterone secretion is questionable, as judged from experiments in vitro [16]. Therefore, a role for participation of these peptides presently does not seem too promising. This pessimism, of course, has to be tempered by the possibility that some other aldosterone-stimulating factor (as yet un-
characterized) could be released in response to metoclopramide from the pituitary or the brain. The aldosterone-stimulating factor that has been isolated by Sen et al. [11] appears to originate from the pituitary. A similar factor could conceivably be involved. Metoclopramide, however, is able to stimulate aldosterone secretion in patients with hypopituitarism [28, 29, 70].

Since the tenet of dopaminergic control of aldosterone has been based heavily on the effect of metoclopramide on aldosterone secretion one must consider alternative possibilities for the mechanism of action of metoclopramide. Metoclopramide could conceivably produce its effect on aldosterone secretion by a non-dopaminergic mechanism. It has been suggested with regard to prolactin secretion induced by metoclopramide, that this effect may be related to a serotonergic effect of metoclopramide [80]. But, in the case of prolactin secretion the role of a dopaminergic mechanism is already firmly established [81, 82] and the proposed serotonergic mechanism may have very little relevance. Besides, it has been shown that metoclopramide has anti-serotonin properties in vitro [40]. Metoclopramide also possesses cholinergic properties [83]. A cholinergic mechanism of stimulation of adrenal steroid secretion at the adrenal or pituitary level could be present [84-86]. As alluded to earlier, adrenal cortical innervation (as in adrenal medulla) may be cholinergic in nature. Thus it is quite possible that metoclopramide-induced rise in aldosterone secretion may also be mediated by a cholinergic rather than an anti-dopaminergic mechanism. Firm evidence as to a physiological role of a cholinergic mechanism on the pituitary-adrenal hormone secretion is not yet at hand.

In conclusion, although the concept of a dopaminergic regulation of aldosterone secretion is attractive the evidence for it is still quite tenuous. The vast majority of observations on which such a thesis has been built rest on the effects of one dopamine antagonist on aldosterone secretion. Because of the complexity of actions of dopaminergic agents and dopamine receptor systems [87] one has to be cautious about the interpretations of any data. The presence of dopamine receptors in the adrenal cells does not necessarily mean that they are involved in a dopaminergic modulation of steroid secretion. Additionally, in the rat and some other species the present evidence suggests that aldosterone-stimulating effects of metoclopramide may not occur directly at the adrenal site. Other mechanisms for the effect of that agent have not been excluded and the action of chemically dissimilar dopamine antagonists with an aldosterone-stimulating effect has not as yet emerged. The logistics of the putative dopaminergic mechanism of action, especially in the adrenal, is even more shaky. The reported attenuation of metoclopramide-mediated aldosterone secretion by dopamine may not be specifically related to antagonism of the dopaminergic property of metoclopramide. Therefore, a convincing case for a physiologically significant role of a dopaminergic mechanism on aldosterone secretion has yet to be made. I should refer the attention of the readers also to an excellent detailed review on the subject by Campbell et al. [88]. In the present review I have tried to focus attention on some of the substantive issues with regard to the dopaminergic mechanism and various alternative possibilities which could explain the basis of the action of metoclopramide, the dopamine antagonist which has given birth to the concept.

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