Control of aldosterone secretion

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Introduction

Much has been learned of the grosser aspects of the control of secretion of aldosterone, the major mineralocorticoid, in the 25 years since its isolation and characterization. There remains little doubt that the main components of the control system are adrenocorticotrophic hormone (ACTH), sodium and potassium status and, arguably the most important, angiotensin II. Other factors may play a minor role. The studies leading to these conclusions have been reviewed (Farrell, 1958; Blair West, Coghlan, Denton, Goding, Wintour & Wright, 1963; Davis, 1967; Fraser, Brown, Chinn, Lever & Robertson, 1969; Müller, 1971; Ross, 1975; Brown, Fraser, Lever, Morton & Robertson, 1977) and need not be considered here. Of more current interest are the mechanisms by which control is exerted at a molecular level and also how the various agents interact with each other in vivo. Another important trend in contemporary research is the careful comparison of the quantitative relations between aldosterone and its stimuli in healthy subjects and in those with various forms of hypertensive disease.

The aldosterone molecule has all the features common to corticosteroids but in addition possesses an aldehyde moiety at C-18. Its biosynthesis in the adrenal zona glomerulosa is summarized in Fig. 1. From this it is clear that the early steps in biosynthesis are common to all 17-deoxy-corticosteroids and that only the final conversion of corticosterone into aldosterone is unique. Location of effects in the 'early' or 'late' sections of the pathway may therefore be important. Secondly, the sequence of events between corticosterone and aldosterone is as yet unclear. It now seems unlikely that free 18-hydroxycorticosterone is the immediate precursor, although adrenal tissue of various types can convert it into aldosterone (see review by Fraser & Lantos, 1978) and a metallo-enzyme–hydroxycorticosterone complex is postulated instead (Ulick, 1976). Thirdly, at several points during biosynthesis the steroid precursor must traverse the mitochondrial membrane, since certain key reactions occur in the cytosol (see Schulster, Burstein & Cooke, 1976). That these intracellular membranes may limit corticosteroidogenesis is shown by the enhancing effect on biosynthesis when adrenal tissue is treated with anti-microtubular agents, which destroy such barriers (Ray & Strott, 1978). In theory, then, the rate of aldosterone formation could be altered by simple effects on single enzyme-catalysed reactions where these reactions are rate-limiting. This might result from an increase in the enzyme concentration or in the availability of substrate in the appropriate compartment. The consequences of accelerating one transformation on the rates of subsequent reactions must also be considered.

In this brief review, the individual stimuli—ACTH, potassium and angiotensin—will be discussed. The direct effect of sodium status on aldosterone secretion (Blair West et al., 1963) will be omitted since wide variations in secretion may occur in the absence of marked changes in circulating sodium concentrations. The importance of sodium status lies in its ability to modulate the effects of other trophins. Finally, some mention will be made of relationships between aldosterone and its stimuli in various hypertensive states.

Adrenocorticotrophic hormone

ACTH is secreted in response to so-called stress (Sayers, 1950) and in circumstances in which...
circulating amounts of glucocorticoid are inadequate. In normal subjects, its secretion is in episodes of variable frequency and amplitude and shows a well-defined circadian rhythm with high plasma concentrations in the early morning and low values at night (Krieger, 1977). The pattern is reversed in nocturnal animals (Meier, 1976). The hormone is rapidly cleared from the circulation (Nicholson, Liddle, Puett & Liddle, 1978). Secretion does not respond to changes in electrolyte status within the physiological range, and ACTH, while it is important in both long- and short-term control, is unlikely to be a specific stimulant to aldosterone, but rather a general stimulant of corticosteroid secretion (see, however, Vale & Rivier, 1977).

ACTH acts early in the biosynthetic pathway at the stage of cholesterol side-chain cleavage, probably by increasing the availability of cholesterol esters within the mitochondria. Cholesterol esterase activity is raised and the increased supply of cholesterol alters the activity of the desmolase-catalysed, side-chain-cleavage reaction (Garren, Gill, Masui & Walton, 1971). The synthesis of a labile protein may be involved (see Farese & Prudente, 1977). ACTH may also influence the binding of cholesterol to cytochrome P450, a prerequisite for mixed function oxidase (steroid hydroxylase) activity. Later hydroxylation reactions, such as that at C-11β, may also be stimulated (see Fraser & Lantos, 1978) and this more general effect may be explained by a reported increase in the amounts of adrenodoxin, another component of mixed function oxidase reactions, in some preparations (Asano & Harding, 1976). Most of these effects are accomplished by the stimulation of adenyl cyclase activity and can be mimicked by cyclic AMP or its derivatives (Schulster et al., 1976), and calcium ions play an important role in the response (Simpson & William-Smith, 1975; Farese & Prudente, 1978). Prostaglandins may also be involved in the action of ACTH (Spät, Siklos, Antoni, Nagy & Szirányi, 1977; Honn & Chavin, 1977). ACTH may affect adrenal blood flow (L’Age, Gonzalez-Luque & Yates, 1970).

Acute infusion of ACTH or stress-induced ACTH release in normal subjects raises plasma aldosterone concentration, although the dose–response curve is less steep than with other corticosteroids such as cortisol (Fraser, Brown, Ferriss, Kennedy, Lever, Mason, Morton, Nicholls, Ramsay, Robertson, Schalekamp & Wilson, 1976). However, Nicholls, Espiner & Donald (1975) found a slightly more sensitive response to infused ACTH than cortisol when plasma ACTH remained within the normal range. Rat zona glomerulosa cells also respond as vigorously to ACTH as to angiotensin II or potassium (Tait, Tait, Gould & Mee, 1974b). The stress-related increase in sheep plasma aldosterone concentration is due almost entirely to ACTH (Espiner, Lun & Hart, 1978).

The nature of ACTH secretion results in fluctuating plasma concentrations and these are closely followed by changes in ACTH-dependent steroids such as cortisol (Gallagher, Yoshida, Roffwarg, Fukushima, Weitzman & Hellman, 1973) and possibly also androstenedione (James, Tunbridge, Wilson & Goodall, 1978). The fact that plasma aldosterone concentrations fluctuate synchronously with those of cortisol (Weinberger, Kem, Gomez-Sanchez, Kramer, Martin & Nugent, 1975) has been taken as evidence of the importance of ACTH in the minute-to-minute control of aldosterone secretion. However, while the rhythmic variations of plasma cortisol are obliterated by suppression of ACTH secretion (with dexamethasone), those of aldosterone persist (Katz, Romfh & Smith, 1975; Weinberger et al., 1975) possibly suggesting that the origin of the rhythm of ACTH and aldosterone is the same, but that that of aldosterone is not mediated by ACTH. Moreover, even normal subjects show some lack of aldo-
Steroid—cortisol synchrony (James, Tunbridge & Wilson, 1976). Nevertheless, although the importance of ACTH in the short term remains equivocal, long-term ACTH insufficiency results in a reduced responsiveness of aldosterone secretion to such stimuli as salt depletion (Ross, van't Hoff, Crabbe & Thorne, 1960).

Long-term ACTH excess, whether therapeutically administered or secreted in pathological quantities from pituitary or bronchial lesions or in subjects with defects of corticosteroid biosynthesis, does not usually cause hyperaldosteronism. Indeed, plasma concentrations or secretion rates are usually low and, where ACTH release can be suppressed, they may be seen to rise (Fraser et al., 1976). In these subjects, the plasma concentrations of the minor mineralocorticoids are high, causing sodium retention and hypokalaemia, and the explanation for this apparently paradoxical behaviour of aldosterone secretion lies in the suppressive effect of sodium loading on the response of aldosterone secretion to ACTH.

In human subjects and in animals depleted of sodium, aldosterone secretion or plasma concentration responds more vigorously to ACTH than in the replete state (James, Landon & Fraser, 1968; Kem, Gomez-Sanchez, Kramer, Holland & Higgins, 1975). In a more detailed dose—response study in the dog, R. D. Gordon, M. G. Nicholls, M. Tree, J. Casals-Stenzel, J. J. Brown, R. Fraser, G. D. Hay, A. F. Lever, P. A. Mason, A. Millar, J. J. Morton & J. I. S. Robertson (unpublished work) infused $1^{-24}$-ACTH at a series of rates after suppressing endogenous ACTH secretion. The gradient of the linear regression relating log ACTH infusion rate to plasma aldosterone was increased by sodium depletion but attenuated by sodium loading. There was some evidence that cortisol was more responsive in the salt-loaded animals, an observation first made by Erlich (1966). Thus long-term exposure to ACTH, indirectly causing sodium retention (Fraser et al., 1976), reduces the sensitivity of aldosterone to the pituitary hormone and also suppresses the secretion of renin, another major trophin (see below). Hypokalaemia, another consequence of long-term ACTH, also modifies steroid secretion.

From time to time the possibility has been raised that the anterior pituitary might assist in the control of aldosterone secretion by means other than ACTH release. Growth hormone, it is suggested, may be important in this respect. This hypothesis has recently been studied in man by McCaa, Montalvo & McCaa (1978), who also summarize previous literature on the subject. They found subjects with isolated growth hormone deficiency to have normally responsive aldosterone secretion. Subjects with panhypopituitarism, on the other hand, had low aldosterone concentrations, which could not be corrected with growth hormone. From this evidence a role for growth hormone seems unlikely.

Potassium

In all species studied, raising the body's potassium content by increasing dietary intake, by systemic or by local adrenal artery infusion, increases aldosterone secretion or excretion rate. The potassium ion is of equal importance to the renin—angiotensin system (Dluhy, Greenfield & Williams, 1977) but induced changes in its concentration are probably not the mechanism for the aldosterone response to either ACTH (Espiner et al., 1978) or angiotensin II. In man, plasma aldosterone concentration failed to respond to severe hypokalaemia in the absence of the octapeptide (Brown, Chinn, Fraser, Lever, Morton, Robertson, Tree, Waite & Park, 1973). Only small changes of plasma potassium concentration are required to alter aldosterone concentrations significantly (Dluhy, Axelrod, Underwood & Williams, 1972; Cooke, Horvath, Moore, Bledsloe & Walker, 1973; Himathongkam, Dluhy & Williams, 1975). Infusion of quantities of potassium too small to alter plasma concentration may increase plasma aldosterone concentrations (Birkhauser, Gaillard, Riondel, Scholer, Vallotton & Müller, 1973).

With the exception of serotonin, potassium is the only known stimulus specific to the zona glomerulosa (Blair West, Coghlan, Denton, Scoggin, Wintour & Wright, 1970; Tait, Tait & Bradlow, 1972; Braley & Williams, 1977). In preparations of adrenocortical tissue in vitro increasing potassium concentrations in the donor animal or in the incubation medium stimulate aldosterone production and also the production of its precursor corticosterone (Boyd, Palmore & Mulrow, 1971; Tait et al., 1972; Williams & Braley, 1977). In vivo, however, stimulation of aldosterone secretion may not be accompanied by increased release of corticosterone (Blair West, Coghlan, Denton, Goding, Munro, Peterson & Wintour, 1962; Boyd et al., 1971) or plasma 11-hydroxycorticosteroids (Cooke et al., 1973), although there is evidence that corticosterone concentrations may rise in the dog (Davis, Urquhart & Higgins, 1963) and sheep (Funder, Blair West, Coghlan, Denton, Scoggin & Wright,
1969). Much of the increased zona glomerulosa corticosterone produced is probably converted into aldosterone, since potassium enhances this conversion (Haning, Tait & Tait, 1970; Boyd et al., 1971).

The effective range of extracellular potassium concentration has been studied by Tait and his colleagues (Haning et al., 1970; Tait et al., 1974b; Tait & Tait, 1976). Their finding that aldosterone production progresses to a maximum at an extracellular concentration of 8-8 mmol/l is in agreement with infusion experiments in vivo in the dog (M. G. Nicholls, M. Tree, J. Casals-Stenzel, J. J. Brown, R. Fraser, G. D. Hay, A. F. Lever, J. J. Morton & J. I. S. Robertson, unpublished work). Experiments in vivo also show that further increases in potassium concentration are inhibitory, but such concentrations are difficult to achieve in vivo. M. G. Nicholls et al. (above) demonstrated a close positive correlation between plasma potassium concentration during potassium chloride infusion and plasma aldosterone regardless of the sodium status of the dogs. Similar results have been obtained in the rat (Corvol, Oblin, Degoulet, Fressnard & Ménard, 1977) but in normal humans Himathongkam et al. (1975) report a non-linear relationship. Studying correlation of circulating ion and hormone may, however, be misleading. Previously it was stated that small quantities of potassium may alter aldosterone concentrations without affecting plasma potassium concentration. Moreover, plasma potassium concentration may be reduced by glucose and/or insulin administration (Farber, Pellegrino, Conran & Earle, 1951), which also affect aldosterone concentrations (Himathongkam et al., 1975), and noradrenaline infusions also have a variable effect on plasma potassium (Todd, Vick & Turlington, 1968). Even mild muscle activity alters plasma potassium concentrations (Farber et al., 1951; Brown, Chinn, Davies, Fraser, Lever, Rae & Robertson, 1970), as does change of posture, and there are also sex differences (Sassard, Vincent, Annat & Bizollan, 1976). Control of potassium metabolism has been reviewed by Stockigt (1977). These changes probably reflect altered potassium distribution between intra- and extra-cellular compartments and on currently available information it is not possible to decide whether plasma, tissue or total body concentration is the best index of 'status' in relation to adrenocortical activity. Plasma or serum concentrations are undoubtedly the most convenient.

The mechanism by which potassium affects aldosterone secretion is not known. In contrast to the physiological effects of changes in sodium status, the renin-angiotensin system is probably not involved except where sodium concentrations are altered (see review by Davis & Freeman, 1976). Indeed, if sodium concentrations are kept constant, potassium administration decreases renin concentration, although, when sodium is not controlled, the natriuretic effect of potassium over-rides this suppression and renin increases. The similarity between the responses to high potassium and low sodium states in the whole animal (Boyd & Mulrow, 1972) and in cell preparations (Domoto, Boyd, Mulrow & Kashgarian, 1973) suggested that potassium might act by including sodium loss. However, the effects of potassium and sodium are separable (Dluhy et al., 1977). Moreover, aldosterone concentrations may respond to potassium loading in the absence of measurable sodium loss (Boyd & Mulrow, 1972) or when a negative sodium balance is prevented (Corvol et al., 1977).

The hypothesis that potassium acts by altering adrenocortical intracellular potassium concentration (Baumber, Davis, Johnson & Witty, 1971; Boyd et al., 1971) had not been borne out by direct measurement (Mendelsohn & Mackie, 1975; Szalay, Bacsy & Stark, 1975; Decorzant, Riondel, Philippe, Bertrand & Vallotton, 1977; Mackie, Simpson, Mee, Tait & Tait, 1977). In contrast to ACTH, stimulation of the adenyl cyclase system is probably not the mechanism (Tait & Tait, 1976), although calcium fluxes and intracellular calcium pool size may be specifically altered by potassium in isolated zona glomerulosa cells (Mackie, Warren & Simpson, 1978). Changes in electrolyte distribution raise the possibility that modulation of membrane potential may determine secretory activity. This is not the case in the zona fasciculata (Matthews & Saffran, 1973) but studies of the zona glomerulosa are required.

Changes in potassium status affect aldosterone biosynthesis at more than one locus (Müller, 1971). Potassium probably stimulates the early pathway (Brown, Strott & Liddle, 1972) and its effect on the conversion of corticosterone into aldosterone has already been mentioned. Zona glomerulosa 18-hydroxylase may be stimulated, possibly at the expense of 11β-hydroxylation (Baumann & Müller, 1972a, b). The most recent approach to this problem is that of McKenna, Island, Nicholson & Liddle (1978a), who used inhibitors to separate the early and late phases of biosynthesis. They treated bovine zona glomerulosa cells with Trilostane, which inhibits 3β-hydroxysteroid dehydrogenase-Δ4-5 isomerase activity and therefore prevents the
further metabolism of pregnenolone. The activity of this early part of the pathway increased as extracellular potassium concentration rose from 0 to 6 mmol/l and less consistently in the presence of further increases up to 12 mmol/l. The late pathway was isolated by inhibiting cholesterol metabolism with aminoglutethimide and adding 11-deoxycorticosterone to the incubation. Conversion into aldosterone was enhanced by potassium up to 6 mmol/l but inhibited thereafter. Thus potassium influences both sections of the pathway but the dose–response characteristics of these effects differ. The authors discuss possible reasons for this and review the relevant literature.

Sodium status controls the magnitude of the aldosterone response to potassium infusion. The slope of the potassium–plasma aldosterone dose–response curve is steepened by sodium depletion and flattened by sodium loading in the dog (M. G. Nicholls et al., unpublished work). In this respect, potassium resembles ACTH and angiotensin II (see below) and possible mechanisms of sensitization are briefly discussed below.

Angiotensin

A comprehensive account of chemical, biochemical, physiological and clinical aspects of the angiotensins is available (Page & Bumpus, 1974). In summary, angiotensin II is a pressor octapeptide generated in the circulation by a two-stage reaction from an α-globulin precursor. An initial release of a decapeptide, angiotensin I, is catalysed by the renal enzyme renin. Converting enzyme in lung and other tissues then catalyses the formation of the octapeptide. The formation of angiotensin II can be prevented by converting enzyme inhibitors and its effects can be antagonized at the target organ by analogues such as Sar1,Ala8-angiotensin (saralasin).

The importance of angiotensin II as an aldosterone-regulating agent has been reviewed extensively (see, for example, Brown et al., 1977). The points of evidence may be listed as follows. There is a close correlation between plasma aldosterone concentrations and those of angiotensin II or renin in most situations although exceptions occur, such as in pregnancy or during the early days of total starvation in sodium-restricted subjects. Plasma renin and therefore angiotensin II concentrations are stimulated by sodium loss and inhibited by sodium loading, as would be required of an aldosterone trophin. Infusion of angiotensin II in vivo or incubation of adrenal cells with the peptide raises aldosterone production. In vivo, some of the rise in plasma aldosterone concentration may be due to reduced aldosterone metabolic clearance rate. In subjects incapable of secreting renin, aldosterone secretion is low, despite often severe hyperkalaemia, but responds to exogenous angiotensin II. Conversely, autonomous hypersecretion of renin is associated with secondary hyperaldosteronism. Saralasin (Agabiti-Rosei, Brown, Brown, Fraser, Trust, Lever, Morton & Robertson, 1979) or converting enzyme inhibition cause a fall in plasma aldosterone concentration. Finally, autonomous hypersecretion of aldosterone is associated with subnormal renin and angiotensin II concentrations.

Despite earlier reports to the contrary, angiotensin II in vivo within the physiological range is a specific stimulus to aldosterone production. Infusion into normal subjects, whether sodium replete or deplete, raises the plasma concentrations of aldosterone and 18-hydroxycorticosterone but not those of other corticosteroids (Mason, Fraser, Morton, Semple & Wilson, 1976; Mason, Fraser, Morton, Semple & Wilson, 1977). In isolated zona glomerulosa cells, increases in aldosterone production are accompanied by parallel rises in the production of its precursors (Tait et al., 1974b; Bing & Schulster, 1977). However, zona fasciculata tissue will only respond to high, unphysiological concentrations of angiotensin II (Bing & Schulster, 1977). It is of interest that if the dose–response relationships of angiotensin II and individual corticosteroids are studied in vivo in man in the presence of a low, constant rate ACTH infusion, positive correlation between angiotensin and zona fasciculata products such as cortisol can be obtained (Mason, Fraser, Semple & Morton, 1979), and that infusion of angiotensin II alone suppresses plasma ACTH (Semple, Buckingham, Mason & Fraser, 1979). Implications and mechanisms of this acute angiotensin–ACTH interaction are discussed by Fraser, Buckingham, Mason & Semple (1978) and may in part account for the apparent specificity of action of the octapeptide in acute experiments.

As for ACTH, the acute and chronic effects of angiotensin II are different. For example, Cowley & McCaa (1976) infused sodium-replete dogs at a low rate for 2 weeks and, although there was an initial rise in plasma aldosterone concentration, normal concentrations were restored within 24 h. There was some evidence of a later increase during the second week of infusion. At pharmacological dose rates, the initial response was greater and,
although concentrations then fell, they remained above control values until the infusion was terminated. Sodium loading attenuated the acute response and plasma aldosterone remained normal thereafter.

In a similar series of experiments, also in sodium-replete dogs, Bean, Brown, Casais-Stenzel, Fraser, Lever, Millar, Morton, Petch, Riegger, Robertson & Tree (1979) tested the responsiveness of plasma aldosterone to acutely infused angiotensin II during a 2-week, low-dose chronic infusion of the same peptide. The effects of the chronic infusion were similar to those reported by Cowley & McCaa (1976) and the dose–response curves for acute angiotensin infusion tended to be less steep after 1 and 2 weeks of chronic infusion, steepening markedly when the chronic infusion was terminated. Discussion on both papers emphasizes the complex nature of these responses. A sodium load affects both potassium metabolism and adrenocortical responsiveness to angiotensin II. Even small increases in aldosterone secretion may, after a time, cause sodium retention and potassium loss. That sodium retention is at least partially responsible for the attenuated response to angiotensin II in these experiments is suggested by the work of Oelkers, Schöneshöfer, Schultzze, Brown, Fraser, Morton, Lever & Robertson (1975) and Oelkers, Schöneshöfer, Schultzze, Wenzler, Bauer, L'Age & Fehm (1978), who infused normal human subjects but prevented changes in electrolyte balance. In contrast to the other studies, aldosterone secretion became more responsive to angiotensin II.

The mechanism of action of angiotensin II and the locus of its effect on the biosynthetic pathway leading to aldosterone is uncertain. It probably affects the early pathway (see Müller, 1971) but evidence of a late pathway effect has been more difficult to obtain (see review by Fraser & Lantos, 1978). Indirect evidence that the 'early' effect is not identical with that of ACTH has been obtained by Lebel & Grose (1976) and Mason et al. (1979). Using inhibitors of corticosteroid biosynthesis as described earlier, McKenna, Island, Nicholson & Liddle (1978b) may have resolved this problem. In the presence of Trilostane, angiotensin II increased bovine adrenal pregnenolone production and, when the tissue was treated with aminoglutethimide, 11-deoxycorticosterone conversion into aldosterone was enhanced. Thus angiotensin II may affect both early and late pathways but the relative importance of the two effects is uncertain. Obviously, pre-eminence of a late effect would go some way to explaining the specificity of angiotensin II but, as emphasized by J. Coghlan in a recent workshop discussion, if the concentrations of the late pathway enzymes are not rate-limiting in vivo, an effect here would be of little physiological significance.

Angiotensin II may not act through the adenyl cyclase system. While it is known that it binds to specific membrane receptors, subsequent events are largely uncharted. Current evidence suggests that zona glomerulosa steroid responses may occur in the absence of changes in cyclic AMP production and that an increase in nucleotide secretion is detectable only after supramaximal stimulation (Petyremann, Brown, Nicholson, Island, Liddle & Hardman, 1974; Tait, Tait, Gould, Brown & Albano, 1974a), but doubts have been expressed as to whether excreted cyclic AMP is the best index of adenyl cyclase activity. In the most recent work on this subject (Bing & Schulster, 1978), it was reported that incubated rat adrenal zona glomerulosa cells gave parallel responses for corticosterone, aldosterone and cyclic AMP to low, physiological concentrations of angiotensin II. They suggest that previous failure to detect this association may have been due to excessive doses of octapeptide or lack of sensitivity of adrenal preparations. The matter remains sub judice.

A heptapeptide derivative of angiotensin II, des-Asp-angiotensin II or angiotensin III, also circulates in the blood of man, dog, rat and probably other species. Its concentration responds to changes in sodium status and it is capable of stimulating aldosterone secretion, although there is some disagreement about the relative potency of the octa- and hepta-peptide (see discussion by Semple, Nicholls, Tree & Fraser, 1978). However, plasma angiotensin III concentrations are much lower than those of angiotensin II in man and the dog (Semple et al., 1978), making its role as an aldosterone trophin less likely. It may be important in the rat. The suggestion that angiotensin III might be formed at the target cell and act as the local effector is unlikely since the demonstration that the octapeptide can be recovered unchanged from incubations of dog adrenal cells (Douglas, Bartley, Kondo & Catt, 1978). The purpose of the specific angiotensin III receptors remains a mystery (Devynck, Pernollet, Mathews, Khosla, Bumpus & Meyer, 1977).

The steepness of the angiotensin II–aldosterone dose–response curve, like those for ACTH and potassium, is enhanced by sodium depletion and attenuated by sodium loading (Oelkers, Brown,
Fraser, Lever, Morton & Robertson, 1974; Holenberg, Chenitz, Adams & Williams, 1974; Nicholls, Tree, Brown, Douglas, Fraser, Hay, Lever, Morton & Robertson, 1978). Several possible explanations have been advanced for this important modulating effect of sodium status. Firstly sodium depletion by dietary sodium restriction takes several days, during which plasma angiotensin II concentrations will be high. This may cause zona glomerulosa hypertrophy. Consequently, when challenged with exogenous angiotensin II, there is more tissue to respond. Some evidence that this may be a partial explanation has been obtained by Oelkers et al. (1975). Secondly, a period of dietary sodium restriction may lead to an accumulation of an essential precursor, which, when angiotensin II is infused, may be converted into aldosterone. Sodium depletion stimulates plasma 18-hydroxycorticosterone concentration to a greater extent than that of aldosterone, and subsequent angiotensin II infusion has a proportionately greater effect on aldosterone (Mason et al., 1977). However, the importance of this 18-hydroxy compound as an aldosterone precursor is questioned (Ulick, 1976). Another possible explanation of these results is that aldosterone and 18-hydroxycorticosterone are alternative products from a common precursor and that sodium status controls their ratio. Finally, there is good evidence that sodium depletion and, incidentally, potassium loading, increases the number of angiotensin II receptors on zona glomerulosa cells, whereas sodium loading has the opposite effect (Douglas & Catt, 1976). The importance of such a mechanism would obviously depend on the number of receptors being a limiting factor in the steroidogenic response.

Modification of control in some hypertensive states

The relationship between aldosterone secretion and its major determinants may be altered in cases of hypertension and in some other diseases. For example, aldosterone secretion is abnormally sensitive to ACTH in primary hyperaldosteronism. As originally described, this condition is caused by an adrenocortical adenoma and is associated with hypertension, low plasma renin or angiotensin II and high aldosterone concentrations. It is now recognized that these symptoms can occur in the absence of an adenoma, the condition then being variously described as idiopathic hyperaldosteronism or adrenocortical micronodular hyperplasia. Subjects with low-renin essential hypertensive have normal aldosterone concentrations (see reviews by Conn, 1977; Ferriss, Beevers, Brown, Davies, Fraser, Lever, Mason, Neville & Robertson, 1978). In many subjects with primary hyperaldosteronism the parallelism between the circadian and episodic pattern of plasma aldosterone and cortisol is even more marked than in normal subjects and plasma aldosterone suppresses to a greater extent during dexamethasone treatment (Kem, Weinberger, Gomez-Sanchez, Kramer, Lerman, Furuyama & Nugent, 1973; Vetter, Berger, Armbuster, Siegenthaler, Werning & Vetter, 1974; Kem, Weinberger, Gomez-Sanchez, Higgins & Kramer, 1976; Mason et al., 1978).

However, not all subjects respond in this way. In a recent study, Wenting, Man in't Veld, Derkx, Brummelen & Schalekamp (1978) identified two categories, those with (group 1) and those without (group 2) parallelism of plasma aldosterone and cortisol. Group 2 failed to lower plasma aldosterone concentrations during short-term (approximately 24 h) dexamethasone therapy. However, similar treatment in group 1 resulted in a significant lowering, although the circadian pattern, with a morning peak, was retained. Plasma aldosterone escaped from suppression after several days of therapy in both groups. Kem et al. (1976) also remarked on this tendency to escape in some subjects with adrenocortical adenomata and also found that plasma aldosterone did not suppress at all in some patients with idiopathic hyperaldosteronism. Conversely, plasma aldosterone concentrations respond poorly to infused angiotensin II in subjects with adrenocortical adenomata. This may be related to their higher degree of ACTH dependence and the inhibitory effect of acute angiotensin II infusion on ACTH secretion. Infusion of angiotensin II in the presence of a low, constant-rate ACTH infusion restores the aldosterone response (Mason, Brown, Fraser & Padfield, 1978).

Finally, the 'sensitivity' of aldosterone secretion to angiotensin II administration has been reported to be altered in hypertension of different aetiologies. Unfortunately, much of this work has been carried out with single doses or infusion rates, whereas a proper distinction can only be made if full dose-response studies are carried out, either by using a wide range of angiotensin II infusion rates and measuring the resulting plasma concentrations of octapeptide and mineralocorticoid or by analysing plasma samples in which the endogenous concentrations of these variables cover as wide a range as possible. The importance of this is discussed by Brown, Casals-Stenzel, Cumming,
Davies, Fraser, Lever, Morton, Semple, Tree & Robertson (1979) and examples of altered angiotensin II–aldosterone relationships are given. For example, long-term exposure to high plasma angiotensin II concentrations, such as in cases of renin-secreting renal tumours and malignant hypertension, displaces the dose–response curve upwards so that higher aldosterone concentrations are associated with a given octapeptide concentration. Conversely, patients with prolonged hypo-reninaemia respond less well than normal subjects to angiotensin. The authors conclude that this latter finding is interesting. The relation of arterial pressure and plasma angiotensin II concentration: a change produced by prolonged infusion of angiotensin II in the conscious dog. Clinical Endocrinology (In press).

Although in cases of primary hyperaldosteronism with adrenal tumours the aldosterone response to angiotensin II is attenuated, those cases with idiopathic hyperaldosteronism or with low-renin essential hypertension have a more vigorous than normal response (Wisgerhof & Brown, 1978; Wisgerhof, Carpenter & Brown, 1978). Subjects with essential hypertension with normal renin also have a brisker than normal response (Davies, Beevers, Brown, Cumming, Fraser, Lever, Mason, Morton, Padfield, Robertson, Titterington & Tree, 1979). Davies et al. (1979) have compared the control of aldosterone in these forms of hypertension. Not unexpectedly, when a tumour is present, the curve relating endogenous angiotensin II and aldosterone concentrations has a negative slope because autonomous secretion, by causing sodium retention, progressively suppresses renin secretion. In low-renin essential hypertension with normal aldosterone concentrations, the slope was positive and steeper than normal. Perhaps the most interesting aspect of this analysis was the finding in idiopathic hyperaldosteronism (micronodular hyperplasia or non-tumorous primary hyperaldosteronism), where the correlation was again positive. The authors conclude that this latter condition more closely resembles essential hypertension than primary hyperaldosteronism with tumour and, moreover, that essential hypertension, low-renin essential hypertension and idiopathic hyperaldosteronism may form a single continuous distribution arbitrarily separated by definition.

References


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