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Central control of aldosterone secretion

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THE CENTRAL CONTROL OF ALDOSTERONE SECRETION

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Some of the recent advances in medicine today are being made in regard to the adrenal steroid aldosterone. Much is known as to its bio-logic activity, but the exact mechanism of action and the control of secretion of this hormone have remained obscure. The central control of aldosterone secretion has been of much interest lately, and it is this particular facet which will be the concern of this paper.

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GENERAL CONSIDERATIONS

HISTORY: Aldosterone is the most recently discovered and most potent steroid secreted by the adrenal cortex in the regulation of electrolyte balance. Almost everyone is agreed now that the site of secretion is the zona glomerulosa of the adrenal cortex.

The hormone was first detected in 1934 by Kendal and Mason as a "sodium retaining fraction" (SRF) in the amorphous fraction from adrenal extracts (10). In 1950 Luetscher and Deming isolated SRF in crude form from human urine. The isolation of crystalline aldosterone from cortical extracts was performed in 1953 by Simpson and Tait who gave the steroid its present name (20,23). Aldosterone was first synthesized in 1955 by Wettstein (23), and it can also be obtained from beef or hog adrenals and from urine of edematous patients. In 1954 Conn described a new clinical syndrome caused by an excessive secretion of aldosterone, and since then many other cases have been recognized. Increased output of aldosterone has also been implicated in nephrosis, cardiac failure, cirrhosis, and possibly essential hypertension.

METABOLISM: Aldosterone is present in only very small quantities in the blood and urine, even in pathologic states. There is good evidence that the hormone is inactivated by the liver and excreted in the urine as the glucuronide (23).

STRUCTURE: Aldosterone is the 18-aldehyde of corticosterone.

PHYSIOLOGY: Aldosterone involves the homeostatic control of

hydrogen, sodium, and potassium ions, and in this respect is thirty times more active than desoxycorticosterone. Secretion causes an increase in urinary hydrogen and potassium ions and a retention of sodium ion. Aldosterone has also been found to depress the Na/K ratio in saliva, indicating that its effects are not limited to the kidneys alone (30). In greater than physiological amounts it produces potassium loss and alkalosis. In contrast to hydrocortisone, evidence to date is against storage or significant protein binding of aldosterone.

Anti-allergic or anti-inflammatory activity of aldosterone has not been demonstrated. In fact it may even block the anti-inflammatory action of cortisol (23).

The latest studies have failed to demonstrate any effect on carbohydrate metabolism.

A digitalis-like action on the myocardium has been demonstrated, which may come into play in situations of cardiovascular stress (17).

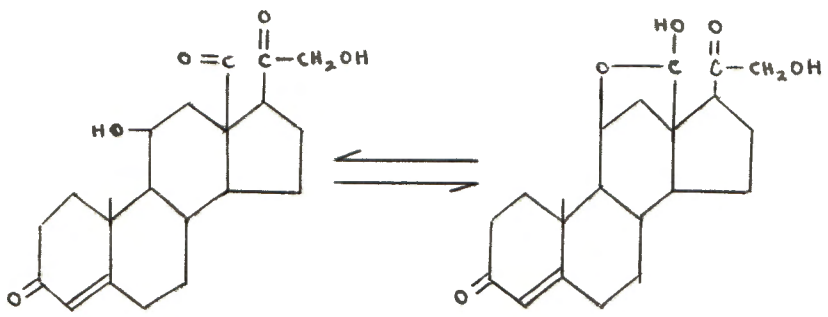

FIG. 1 Structure of aldosterone.

FACTORS INFLUENCING ALDOSTERONE SECRETION

The factors which alter aldosterone secretion are many, but the means by which alterations occur are still not readily explained. The more important regulatory factors will be mentioned briefly.

(1) Several workers are of the opinion that changes in serum sodium are the most important stimuli to aldosterone secretion. It has been shown that sodium restriction leads to an increase in urinary aldosterone while high sodium intake causes a decrease in aldosterone levels (10). How changes in the sodium content of the body fluids are recognized by the organism is not known, but sodium chemo-receptors may be present in the vascular system or brain stem similar to those chemo-receptors associated with the glossopharengeal nerve (17). Thus far, however, none have been described.

(2) The other leading school of thought believes that the volume of the extra-cellular fluid compartment rather than sodium per se is the most important mediator in the regulation of aldosterone secretion (1). The subject of volume receptors has received considerably more study, and most investigators adhere to this hypothesis. Luetscher has suggested that a dual "feed-back" mechanism exists between ADH and aldosterone for the normal control of water and sodium homeostasis.

(3) Right atrial distention in dogs depresses aldosterone secretion suggesting a reflex system based on changes in circulating blood volume, and elicited by receptors in the atrial wall (31). Constriction of the inferior vena cava has been found to cause an elevation in aldosterone

secretion (13). It is believed that this latter procedure decreases the volume of blood entering the right atrium, and the elevated aldosterone level is elicited by the same mural receptors.

(4) Serum potassium content has the opposite effect of serum sodium content, and it is generally believed that the potassium ion plays a minor role.

(5) Emotional excitement and anxiety increases aldosterone output (24). This finding suggests that descending pathways from higher centers may modify the activity of the brain stem areas involved in aldosterone regulation.

Whatever the nature of the receptor system may be, it is obvious that an effector system must exist by which the zona glomerulosa is stimulated to secrete aldosterone in response to changes in the internal environment. This effector system will be the topic for further discussion.

The existence of central nervous system regulation of electrolytes has been suspected for some time. As early as 1951 Viar and his associates suggested central nervous system control of sodium metabolism. They found that in healthy individuals excretion of sodium is decidedly less in the sitting position than in the recumbant position and that the difference can be partially overcome by compressing the neck veins with a blood pressure cuff (25,42). This suggested to them that alterations in sodium excretion are perhaps brought about by way of intracranial receptors activated by a change in extravascular fluid volume within the cranial cavity.

Of special interest clinically is the cerebral salt-wasting syndrome associated with encephalitis, bulbar poliomyelitis, or cerebral vascular accident described by Welt (43). In this syndrome there is increased excretion of salt in the urine but no evidence of pituitary or adrenal dysfunction or intrinsic renal disease. It is possible that damage to an aldosterone-regulating center is related to the altered electrolyte metabolism seen in this condition.

RELATION OF THE PITUITARY TO ALDOSTERONE SECRETION

Several years before aldosterone was discovered, Swann (40) and Ingle first postulated that the zona glomerulosa secreted an active steroid affecting electrolyte balance that was relatively independent of the adenohypophysis. Their hypothesis was based on the fact that changes associated with "defective salt and water metabolism" of the adrenalectomized animal were not found to occur in hypophysectomized animals. In correlation with this, Deane and Greep observed in the forties that following hypophysectomy, while the rest of the adrenal cortex atrophies, the zona glomerulosa is seen to persist and maintain secretory function as evidenced by normal appearing mitochondria, golgi apparatus, and lipid content (6). While Houssay was apparently the first to notice that the zona glomerulosa does not atrophy after hypophysectomy (13), it was the former investigators who laid out the concept that this region of the adrenals was not dependent on the pituitary-adrenal axis.

The independence of the zona glomerulosa from the adenohypophysis has since been substantiated by a considerable amount of experimental evidence. None the less, our knowledge is still somewhat incomplete on the importance of specific anterior pituitary hormones in the control of aldosterone secretion. Rauschkolb, et.al. have done considerable work in the dog, and when these workers removed the pituitary, aldosterone could be isolated from adrenal venous blood at near normal levels, with only a slight decrease, while the output of the other steroids fell to the expected low levels (34). Because there is some noticeable decrease in aldosterone levels after hypophysectomy, these findings indicate that although aldosterone does not seem to depend on complete control by ACTH, perhaps a factor or factors elaborated by the pituitary may be necessary to maintain the control levels of aldosterone. These same investigators observed that ACTH administration in intact dogs produced a slight increase in aldosterone in adrenal venous blood (8), further indicating that a pituitary factor may be involved in maintaining optimum levels of aldosterone. This has been substantiated by other workers who have obtained similar results (8,37,38). When urinary aldosterone levels are measured, several investigators have found that ACTH administration elevates aldosterone to some extent in the urine (41).

In hypophysectomized rats the output of aldosterone varies in response to changes in electrolyte intake, suggesting that the pituitary is not essential for adrenal response to electrolyte changes. Suppression of ACTH by long term cortisol administration has no significant

effect on aldosterone secretion (9). Why aldosterone levels should be within the normal range following cortisone suppression, yet show some reduction after surgical hypophysectomy may, according to Farrell, be due to damage during hypophysectomy of a nearby structure acting as the primary regulator of aldosterone secretion. ACTH has also been found to stimulate steroidogenesis in tissue incubates of the zona fasiculata and zona reticularis but not in tissue incubates of the zona glomerulosa (39), although on occasions this has been variable depending on the preparation used (22). It is also known that patients with panhypopituitrism have normal levels of urinary aldosterone (27). As mentioned earlier, with constriction of the thoracic vena cava aldosterone secretion increases, however, cortisol secretion falls. The dichotomy of response is interpreted as indicating that the aldosterone secretion is not mediated by ACTH (13). In addition, secretion of cortisol and aldosterone is effected differently after certain brain stem coagulation lesions in cats, suggesting different centers of control (32).

Finally, aldosterone secretion is elevated in the acutely stressed animal, probably due at least in part to an action of the ACTH liberated by stress, since hypophysectomy prevents this (26). No doubt this effect is independent of the mechanism regulating aldosterone secretion in response to changes in dietary sodium and potassium. Ganong points out that cannulation of the adrenal vein is an acute stress, and in determining aldosterone levels the effect of ACTH secretion must be

considered when using this technique (19).

The precise role which the pituitary plays awaits further investigation, but in general the effect of ACTH on aldosterone output is unimpressive, and that the adenophypophysis is not the primary regulator of aldosterone secretion seems to be well supported. It is likely that ACTH provides important support for aldosteroidogenesis but does not necessarily play an initiative regulatory role. It is also entirely possible that increased aldosterone production by ACTH may result from conversion of excess corticosterone to aldosterone (5).

CENTRAL CONTROL OF ALDOSTERONE SECRETION

Since the zona glomerulosa seems to be largely exempt from adenohypophyseal control, the question then arises: How is this endocrine tissue controlled?

A tropic hormone for the secretion of aldosterone was originally postulated by Rauschkolb and Farrell in 1956, but so far it still remains to be isolated in pure form and chemically characterized. These workers recognized that there was indirect evidence for a cephalic structure concerned with regulation of aldosterone secretion and that a tropic factor was very likely (8,34,35). In some preliminary experiments to determine if aldosterone secretion was under central hormonal control, they removed the heads of several dogs, maintaining the trunk under approximately normal conditions of blood pressure, temperature, and oxygen saturation, and obtained a profound fall in the rate of secretion

of aldosterone as determined in adrenal venous blood. If however the carotid arteries and jugular veins were kept intact, the dissection otherwise being the same, the output of the steroid was normal (35). When the spinal cord, sympathetic trunks, and vagi were transected, there was no diminution of aldosterone secretion. This work suggests strongly that the secretion of this steroid is dependent upon a hormonal substance released from a cerebral structure.

In further experiments these same workers found that when brain substance was removed rostral to the corpora quadrigemina, there was a marked fall in aldosterone secretion, but decortication alone had no effect. There is further evidence to substantiate a central area of control in this region. It was shown that coagulation lesions of the ventral diencephalon in the cat cause a significant reduction in the rate of secretion of aldosterone (and also a decrease in cortisol secretion). Similar lesions involving the caudal diencephalon are even more effective in reducing aldosterone secretion. With removal of the entire diencephalon, decreased aldosterone levels are quantitatively greater than with total hypophysectomy. In addition, midbrain lesions extending into the rostral pons cause a significant increase in aldosterone secretion (32). This would suggest the existence of an inhibitory area. It is important to mention however that Ganong and his workers have failed to obtain changes in serum or urinary sodium and potassium in dogs with chronic rather than acute ventral hypothalamic lesions, even when the dogs were placed on a low sodium and

high potassium diet (19). Davis and associates have pointed out that it is very difficult to produce lesions in the diencephalon without destroying at least part of the hypophysis or compromising its blood supply (4). In such an event, the results would be incorrectly interpreted as stemming from destruction of diencephalic tissue, when destruction of hypophyseal tissue could be the cause.

Nevertheless, Farrell made a tentative conclusion that these experimental results point strongly to a humoral agent arising in the head, probably in the region of the caudal diencephalon, having a tropic effect on the zona glomerulosa. This agent was first called "glomerulotropic hormone" (GTH), or "glomerulotropin". The name was later changed to "adrenoglomerulotropin" to assuage renal physiologists who felt that the first name implied action on the glomerulus of the kidney. The initials GTH have been kept however, rather than AGTH, to avoid confusion with ACTH. According to Farrell the controlling center in the diencephalon secretes adrenoglomerulotropin (possibly in part by way of the pituitary), receives stimulatory and inhibitory impulses from receptors in the periphory, and is influenced by other parts of the brain stem (10).

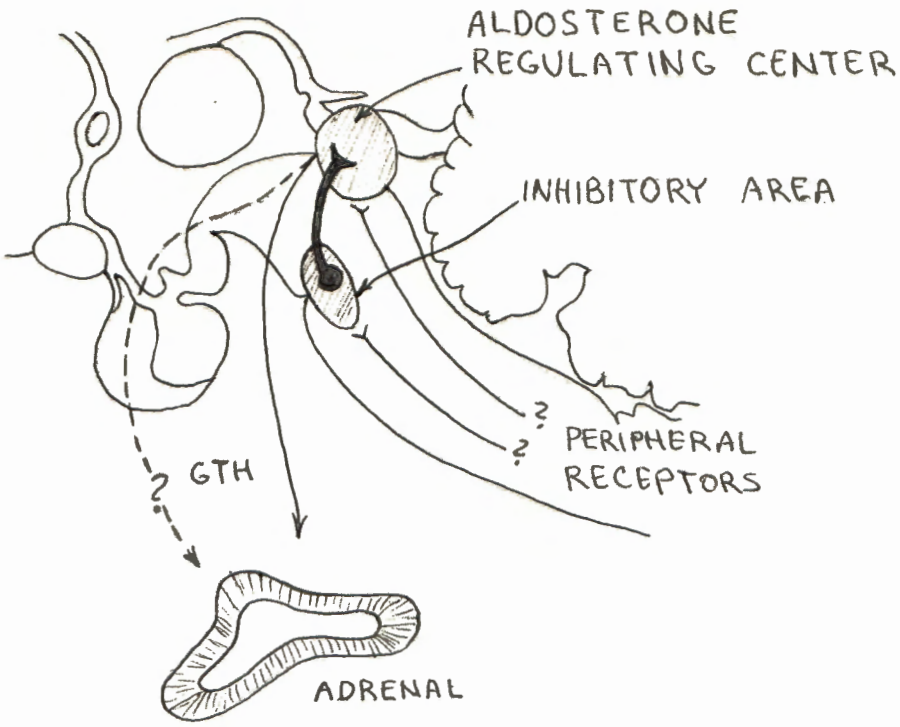

FIG. 2 Postulated neuroendocrine mechanism for the regulation of aldosterone secretion. (Farrell, G. L., Physiol. Rev. 38:709-28, Oct. 1958.)

FURTHER EFFECT OF ACTH ON ALDOSTERONE SECRETION

One must attempt to explain, if possible, the conflicting reports resulting from the variable effect of ACTH on aldosterone secretion and sodium retention. One explanation for such variability is that ACTH stimulates production of other steroids which have some salt-retaining properties, and some urine extraction methods used remove all biologically active steriods, not just aldosterone alone (28). In addition, ACTH as it is generally prepared can be separated into a variety of chemical components, all of which have ACTH activity (2,7,33). Two of these components have been analized for steroidogenic activity in the decerebrate dog, the $delta_1$-corticotropin and the beta-corticotropin. The first compound is several times more potent in stimulating aldosterone

secretion than is the second (11). The variable response of ACTH can also be explained then by the possibility that different ACTH preparations contain varying amounts of the $delta_1$ and beta-corticotropins. The question arises: Why should an adrenoglomerulotropic factor be obtained from pituitary tissue at all, if as it is generally held, aldosterone secretion is independent of the pituitary? A possible answer is that $delta_1$-corticotropin is the postulated GTH. It is also possible that both fractions contain GTH as a contaminant but to different degrees. This could occur if GTH were released through some part of the pituitary, as has been mentioned earlier. Electrophoretic studies of the $delta_1$-corticotropin used reveal that it is not a single substance, but contains four other minor components (11). An alternate possibility is that ACTH or another factor originating in the pituitary is necessary for the optimal action of GTH. This opinion has also been alluded to earlier. Finally, it is possible that ACTH and GTH overlap in their physiological activities, as is the case with oxytocin and ADH. Since the latest studies have demonstrated that beta-corticotropin is a pure compound, its aldosterone stimulating activity could hardly be due to contamination, but rather in fact to an overlap of activity.

NEURAL CONTROL

Fleming and Farrell have transplanted the adrenal gland into the thighs of three dogs and found that the secretion of aldosterone was not significantly different from that of glands in situ (18). From this it

can be concluded that the nerve supply to the adrenal gland is clearly not necessary for aldosterone secretion.

GROWTH HORMONE

Growth hormone has been found to increase urinary aldosterone in man, however, the possibility of GTH contamination had not been ruled out (27). With more purified growth hormone extracts the same workers did not observe an increase in aldosterone secretion (28). Singer and Stack-Dunne have also observed that growth hormone did not significantly modify the rate of aldosterone secretion, and since there are still substantial levels of aldosterone in most animals after hypophysectomy, the stimulatory effect of growth hormone is questionable. Furthermore, Beck has cited one patient with acromegaly who had normal levels of circulating aldosterone, which were maintained after hypophysectomy.

MELANOCYTE STIMULATING HORMONE

Alpha and beta-MSH have not been found to have an effect on steroid secretion (5).

ADRENOGLOMERULOTROPIN

After formulating the existence of a tropic hormone specific for the zona glomerulosa, Farrell and his co-workers proceeded to localize its synthesis and to isolate it if possible. Direct evidence for the postulated hormone was first demonstrated by assaying neutral saline extracts of beef diencephalon in the decerebrate dog with the pituitary

and pineal glands also removed (12). Extracts of whole diencephalon produced an elevation of aldosterone levels but were free of ACTH-like activity. When the diencephalon was divided into anterior and posterior parts, the posterior portion containing the pineal gland had the greater activity. Assay of pineal tissue separately revealed that most of the greater activity was present specifically in the pineal gland. A crude acetone extract of pineal tissue has also been assayed in the decerebrate dog and found to markedly stimulate aldosterone activity (14), but again has no effect on cortisol secretion. When this acetone extract was fractioned between water and hexane, the glomerulotropic activity was found to be contained in the hexane fraction, indicating that the substance is lipid in nature, or associated with a lipid-soluble material. An attempt to isolate the hexane extract by chromatography on a florisil column resulted in a many-fold purification, but efforts at obtaining a single component have been hampered by instability. So far, there are no clues as to the cause of this instability, and because the pineal extract has not been isolated, precise chemical characterization has not been possible. The fact that the substance does not have an effect on cortisol secretion substantiates the hypothesis that it is quite distinct from ACTH.

It has also been found by infusing the decerebrate dog with another eluate of the chromatograph of the pineal extract that secretion of aldosterone is inhibited. Assay of the same eluate for inhibitory activity in the intact dog yielded similar results. Secretion of

cortisol was also inhibited but to a lesser degree. One can speculate from this that there is an antisteroidogenic substance normally secreted by the pineal gland which participates in regulation of steroidogenesis.

Since GTH is found in pineal extracts it would seem that pinealectomy would result in cessation of aldosterone secretion, but this is not the case. Pinealectomy results in only temporary suppression of aldosterone secretion, which indicates that the pineal body is not required for synthesizing aldosterone (15). It is unknown whether the slight depression of aldosterone secretion resulted from removal of the pineal body per se, or whether it was due to disruption of near by structures. The latter alternative seems more likely however, since some pinealectomized dogs respond to sodium depletion by an increased aldosterone secretory rate. Experimentally then, it appears that the consequences of pinealectomy are a removal of inhibitory rather than stimulatory influences.

Confusion here may stem from the possibility that two glands are involved. Another glandular structure in the same area of the brain is the subcommissural organ, which is related to water balance and to control of aldosterone secretion. Gilbert has shown that after ablation of the subcommissural organ in rats, drinking ceases and death by dehydration may result. Paradoxically, subcutaneous injections of extracts from this region also depress water intake, but recovery occurs soon unless the rats have been adrenalectomized or hypophysectomized (21). Gilbert states that the subcommissural organ may act

as the effector responding to stimulation of the "volume receptor", or it may be the volume receptor itself. Moreover, as previously stated, coagulation lesions in the midbrain of the cat at the level of the anterior opening of the cerebral aqueduct into the third ventricle have been found to reduce the output of aldosterone (17). Although these lesions did not involve the pineal in all cases, the subcommissural organ was disrupted in all cases producing a decrease in aldosterone secretion. This points to the possibility that stimulatory influences arise in the subcommissural organ. Effective lesions could also have involved nerve pathways leading to other areas of the brain concerned in steroid regulation.

To further establish this region of the brain as the source of GTH, the vein of Galen was cannulated (which drains the pineal as well as the anterior midbrain and posterior thalamus) and the blood infused into decerebrate assay animals at the same rate of flow as that from the vein of Galen. When this was done, aldosterone secretion was restored. There was no effect however on cortisol secretion, indicating an absence of ACTH. This appears to establish without a doubt some structure drained by the vein of Galen as the site of GTH secretion (16). A reasonable possibility is that GTH secreted by a structure lying ventral to the pineal, and it is present in pineal tissue because it is either stored there or because some of the secretory tissue is included in the pineal at the time of collection.

Luetscher and his workers have evidence for a factor from human

plasma and urine which selectively stimulates the synthesis of aldosterone by the rat adrenal in vitro. It remains to be seen whether this substance is the adrenoglomerulotropic hormone of Farrell's.

Further work is now being carried out in Farrell's laboratory, and he suggests that the control of aldosterone involves an excitatory inhibitory system which is comprised of an interplay between corticotropin, adrenoglomerulotropin, and anticorticotropin. He offers the following theoretical concept regarding the locus of action of GTH: The ubiquitous action of ACTH in steroidogenesis can be explained by its action early in the synthetic chain. GTH is postulated to act distal to a branching of the chain, and would in this way influence aldosterone synthesis but have no effect on cortisol synthesis. Maintainance of aldosterone secretion in the presence of a decreased synthesis of precursors following hypophysectomy could be due to a compensatory increased GTH secretion. On the other hand, maintainance of very high levels of aldosterone may require the presence of ACTH. The action of the inhibitor would be prior to the point in the synthetic chain where the separation of pathways occurs, since it inhibits secretion of both steroids (16).

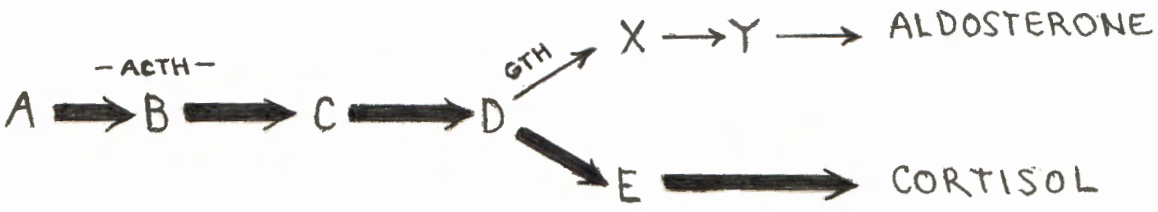

FIG. 3. An hypothesis as to the relationship between GTH and ACTH. GTH is postulated as stimulating aldosterone from ACTH dependent precursors along a branch in the synthetic chain. (Farrell, G. L., Fed. Proc. 19 : 601-4 (July) 1960).

It may not be surprising if GTH proves to be a paleontologically older regulator which was possessed by very early forms of life. The fact that lesions in an older part of the brain are important gives support to this concept. The role of ACTH may be a more subtle and more sophisticated recent development which modulates the system for more complicated situations.

SUMMARY

The most recently discovered adrenocortical steroid aldosterone was first recognized in 1934 in the "amorphous fraction" of adrenal extracts, but it was not until 1950 that it was isolated from human urine. Its synthesis followed rapidly, and in 1954 a new syndrome of excess aldosterone secretion was described by Conn. The steroid is a mineralocorticoid causing urinary sodium retention and potassium and hydrogen ion loss. It has a minimal effect on the inflammatory process or carbohydrate metabolism.

Several factors play a role in the control of aldosterone secretion. The most important of these are serum sodium and potassium levels and extracellular fluid volume.

Early evidence indicated that aldosterone output was independent of the pituitary, because following hypophysectomy there was maintainance of electrolyte balance and lack of atrophy of the zona glomerulosa.

The concept of separate regulation is supported by the finding that serum aldosterone levels are well maintained after hypophysectomy and

in patients with panhypopituitarism, and furthermore ACTH administration causes only a minimal increase in aldosterone output. Suppression of ACTH by the injection of cortisone does not alter secretion of aldosterone significantly. In summary, from all of the evidence it is clear that the pituitary is not the primary regulator of aldosterone secretion but seems to play some role in maintaining optimum physiologic levels of aldosterone.

Evidence has been obtained that ablation of the diencephalon or lesions placed in the posterior diencephalon markedly reduce aldosterone secretion. It has been postulated by Farrell that a humoral agent "adrenoglomerulotropin", or GTH, is released from the diencephalon to stimulate aldosterone synthesis. Extracts of pineal tissue located in the diencephalon have been found to elevate aldosterone levels but have no effect on cortisol secretion. Since this extract is hexane soluble it is thought to be a lipid, although it has not been purified in quantities sufficient for precise chemical analysis. A substance which inhibits steroidogenesis has also been extracted from pineal tissue, and it has been suggested that there is an interplay of the stimulatory and inhibitory substances in electrolyte homeostasis. The effect of ACTH on aldosterone production is explained by the fact that this hormone acts on precursors of aldosterone and cortisol early in the synthetic chain.

CONCLUSION

(1) The history of aldosterone and its physiologic properties are mentioned briefly.

(2) The control of the secretion of aldosterone is discussed with special emphasis placed on central nervous system control. The role of the pituitary is also analyzed in this respect.

(3) A complete report of the experimental work concerning a tropic substance produced by the diencephalon and effecting aldosterone secretion is presented.

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