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Hormonal Interactions

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Regulation of Catecholamine Metabolism in the Sympathetic Nervous System

CHAIRMAN'S REMARKS

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INTERACTIONS between catecholamines (CA) and other hormones have long been known, or at least suspected, and with increasing knowledge of the mechanism of action of hormones these interactions gradually tend to become more precisely defined and interpreted.

Historically such interactions have been noticed early between CA and the thyroid and insulin systems, probably because of the fairly obvious symptomatic and functional interrelationships (8). In this field as in many others the discovery of the cyclic adenosine monophosphate (AMP)-system has greatly aided in the elucidation of the mechanisms. Thyroid-catecholamine interrelations have been discussed in detail by Waldstein (25). Recent studies by Rosenqvist *et al.* (21) seem to indicate that the lipolytic effect of norepinephrine (NE) is reduced in hypothyrotic states in man, apparently due to an altered balance in sensitivity of the *alpha-* and *beta*-adrenergic receptors in the subcutaneous adipose tissue. Thus the *alpha*-adrenergic response which leads to inhibition of cyclic AMP formation is increased during hypothyrosis while the *beta*-adrenergic response is largely unaltered, causing increased inhibition of the synthesis of cyclic AMP and of lipolysis. The reduced stimulating effect of NE on the synthesis of cyclic AMP in the subcutaneous fat seems to be reversed in part by triiodothyronine. Moreover, prostaglandin E_1 (PGE_1) could partly restitute the sensitivity of the hypothyrotic tissue toward the lipolytic effect of NE, suggesting an interaction with this hormone. This is also borne out by the finding of Paoletti *et al.* (18) that the antilipolytic effect of PGE is more marked in hyperthyroid rats. An increased response to *alpha*-adrenergic stimulation in hypothyrotic states has also been demonstrated for the rabbit aorta. It is believed that this kind of effect of thyroid hormones is localized to the cell surface and is an example of what has been termed "tuning" of the receptors.

In hypothyrotic states it has also been noticed that NE turnover is accelerated (15) while it is decreased in thyroxine(T_3)-treated animals. These alterations have

corollaries in the central nervous system (CNS) with implications for psychiatry, particularly endogenous depression, where catecholamines are generally believed to play an important role. This view receives some support by the finding that low doses of T_3 potentiate the antidepressant action of imipramine. As regards the metabolism of NE in the CNS, the conversion of labeled NE is decreased in the brain of hyperthyroid rats and is increased in hypothyroid rats (15, 20).

Recent studies have shown increased tyrosine hydroxylase activity in the midbrain of thyroidectomized rats but no change in the thyroxine-treated animals (4). This is in harmony with the finding of increased conversion of labeled precursor to NE in the thyroidectomized rats. It has been suggested that decreased activity of the adrenergic receptors may cause a compensatory increase in tyrosine hydroxylase activity by a feed back mechanism. In the CNS thyroxine apparently causes sensitization of the receptors to NE and increased motor activity.

Studies by Axelrod, Kopin and Wurtman have indicated that some of the interaction effects observed depend on changes in amount or activity of metabolizing enzymes. Thus thyroid hormones can influence both monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). A few minutes after a dose of epinephrine the amount found in the hyperthyroid rat heart was considerably smaller than in the control (29). A study of the metabolism of tritiated epinephrine *in vivo* in the hyperthyroid rat heart showed a decrease in the cardiac content of all the main metabolites, while they were increased in hypothyroidism.

Hypophysectomy in rats also caused a 2-fold increase in turnover of cardiac NE. This could be restored to normal by administration of thyroxine and adrenocorticotropic hormone (ACTH) together indicating that turnover of NE in the heart is dependent upon these hormones. A long-lasting ganglionic blocker (chlorisondamine) decreased the NE turnover in hypophysectomized rats to normal values, which suggests increased sympathetic activity in these animals (14).

Interactions between corticosteroids and CA are incompletely known although several observations suggest that they occur at different sites and influence various functions. It is frequently observed that vascular reactivity to CA is increased after administration of corticosteroids *in vivo* (1, 23). The poor response to motor nerve stimulation in the adrenalectomized cat is markedly restored by small doses of CA (3).

It has also been claimed that circulating glucocorticoids are necessary for the CA to exert their full free fatty acid mobilizing action. This may be another example of "tuning" effects of one hormone on the receptors for another hormone.

Some older studies have indicated an altered excretion pattern of the CA as a result of administration of ACTH in man. After moderate doses of ACTH the norepinephrine excretion in urine decreases, whereas epinephrine excretion shows a slight increase leading to a greatly increased percentage of epinephrine. This shift in balance between the two amines is also noted after cortisol, but not with deoxycorticosterone (DCA) (6, 17).

The juxtaposition of adrenal and cortical tissue in the adrenals has suggested an interaction between catecholamines and cortical hormones. Evidence for such an interaction has been presented in the now classical studies by Wurtman and Axelrod (30). After hypophysectomy in rats the epinephrine content of the adrenal medulla is decreased in rats and at the same time the phenylethanolamine-N-methyl transferase (PNMT) activity falls off. ACTH as well as the potent glucocorticoid dexamethasone increased the PNMT activity to about normal in the rat, whereas mineralocorticoids were ineffective. Another interesting interaction between CA and corticoids is a decreased ability of the adrenergic nerve terminals to retain CA during DCA-hypertension as observed by Landsberg and Axelrod (14). This effect may be related to some alteration in the axon membrane, or in the vesicles themselves. Thus in rats treated with sodium chloride and DCA the NE content decreased in the heart and several other organs. The half-time of administered ^{3}H-NE fell from 19 hr to 13 hr in the hearts of DCA-salt-treated animals, and the specific activity of the granular fraction fell considerably faster than in the controls (13). Sodium depletion on the other hand increased the retention of NE in the heart. The effect of high salt and DCA was abolished after administration of chlorisondamine. These experiments suggest that sodium is an important factor in determining the storage in the NE particles and indicate that the effect is mediated by nerve impulses.

Changes in the CA content of various organs as a result of hormonal influences have been reported from numerous studies. During pregnancy and different stages of the sexual cycle the endogenous epinephrine content of the uterus shows marked alterations (28) and administration of progesterone lowers both content and concentration of epinephrine in the rat uterus (22). Hormone dependent preponderance of *alpha-* or *beta*-receptors in the rabbit uterus have been reported (27). The capacity of binding epinephrine is greatly increased in estrus as compared to diestrus.

Metabolic interactions between catecholamines and insulin have been described, with oxygen consumption of minced skeletal muscle as main parameter. Under certain conditions both epinephrine and insulin plus glucose increase oxygen consumption or accelerate the decolorization of certain dyes in minced muscle. The enhancing effect of one or the other of these hormonal factors is antagonized by the other, suggesting a common denominator in the metabolic chain. Glycerophosphate proved to be an efficient substrate in these experiments (5). More recent studies suggested that cyclic AMP is one factor which is influenced in opposite directions by these hormones. Thus cyclic AMP is decreased by insulin in adipose tissue and liver whereas an increase is observed with epinephrine. An inhibitory action of epinephrine on insulin secretion, which has been suggested some 40 years ago, was definitely proven by radioimmunoassay methods (31). Norepinephrine and dopamine also inhibit the glucose-induced insulin release (19). It appears that epinephrine has a dual action on the *beta* cells of the pancreatic islets consisting in an inhibitory action on insulin secretion by *alpha*-receptor stimulation and increased secretion by *beta*-stimulation. The *beta*-blocker *l*-propanolol accordingly lowers the basal plasma insulin levels in

normal mice to about 50% (16). *alpha*-Adrenergic blockers like phentolamine on the other hand increase the plasma insulin level.

As shown by Falck and Hellman (7) pancreatic islets of a variety of animals and man contain 5-hydroxytryptamine and dopamine. If the old finding that *l*-dopa induces hyperglycemia is attributable to a dopamine action on the pancreatic islets, the endogenous dopamine in the *beta*-cells is likely to exert a physiological inhibition of the insulin release.

Examples of hormonal interaction involving the CA have been offered by recent studies on the action of prostaglandins. Thus the antagonistic action of PGE compounds on the lipolytic action of CA has been repeatedly demonstrated *in vivo* and *in vitro* (2, 18, 24). This interaction is apparently connected with the formation of cyclic AMP.

Adrenergic neurotransmission is also inhibited by PGE compounds as first demonstrated by Hedqvist and Brundin (10) and by Hedqvist (9) on the release of NE from the perfused spleen, after splenic nerve stimulation. The same phenomenon is observed on the isolated rabbit heart (26) and on the isolated guinea pig vas deferens (11). Since in the isolated vas deferens PGE increases the response to NE it is concluded that the inhibition observed with low concentrations of PGE is a prejunctional phenomenon and due to inhibition of transmitter release. The increased release of NE and dopamine-β-hydroxylase from the isolated vas deferens, induced by calcium in the nerve-stimulated preparation, is also inhibited by PGE_1 (12). Certain observations seem to indicate that the degree of mobilization of calcium plays an important role for the inhibitory action of PG on adrenergic neurotransmission.

As to the type of interaction, some of them involve the process by which one hormone is secreted or released from its production site, as for example the enhancing effect of CA on the release of antidiuretic hormone (ADH), or the action on insulin release.

Other interactions between the CA and agonists of hormonal character appear to occur at the cell receptor level. In some instances the common denominator appears to be cyclic AMP. The modifying effect of one hormone on the action of a second one presumably involves different receptors which, when activated, may have some action in common. "Tuning" of a receptor or modifying its reactivity may provisionally serve as a description for the kind of action exerted by certain hormones which thereby appear to interact with others. The nature of this "tuning" is not known, but it presumably involves structural changes including allosteric effects in the macromolecules which normally react with certain hormones, causing secondary actions on ion transport and induction of certain metabolic processes which determine the target cell response.

From these brief remarks and somewhat arbitrarily chosen examples it seems clear that interaction between CA and other hormones is a common phenomenon and indeed not unexpected. In a few instances it has been possible to bring the interaction fairly close to the molecular level; in other instances this is not yet the case. With increasing knowledge of interactions between single hormones and the macromolecular system in the receptor areas it will no doubt be possible

to better understand how the hormones interact with each other. The use of uniform cell systems, perhaps with cloned cells, may prove useful for this purpose.

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