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STUDIES ON POLYPEPTIDE RECEPTORS
A CRITICAL VIEW ON THE MECHANISM OF ACTH ACTION

R. SCHWYZER

Summary

Recent work on ACTH receptors in adrenal cells and adipocytes is reviewed. It is suggested that ACTH acts on two types of receptor: an adenylate cyclase receptor and another one that helps to guide cAMP into the correct compartment. The introduction of the term holoreceptor to indicate a unit that is recognized by the hormone and is able to produce a measurable effect, and of the terms discriminator, transmitter and effector to indicate the functional subunits of the holoreceptor is suggested as a measure enhancing clarity and flexibility of communication in this very complex field.

Zusammenfassung

Die Ergebnisse neuerer Arbeiten über ACTH-Rezeptoren von Nebennierenrindenzellen und Adipozyten werden schematisch zusammengefasst. ACTH scheint danach auf zwei Typen von Rezeptoren zu wirken: einen Adenylat-Cyclase-Rezeptor und einen noch unbekanntem, der dazu dient, cAMP in das richtige Zell-Kompartiment zu schleusen. Der Terminus "Holorezeptor" wird eingeführt, um eine funktionelle Einheit zu bezeichnen, welche einerseits durch das Hormon erkannt und stimuliert wird und andererseits eine messbare hormonale Wirkung erzeugt. Die funktionellen Untereinheiten des Holorezeptors werden Diskriminator, Transmitter und Effektor benannt. Die vorgeschlagenen Bezeichnungen dürften die Verständigung auf diesem komplexen Gebiete vereinfachen und eindeutiger gestalten helfen.

Introduction

The study of polypeptide hormone receptors is presently one of the most fascinating and rapidly moving subjects of molecular biology. An understanding of their biogenesis, structure,

and function is not only of fundamental interest for medicine, but practical aspects are already becoming evident, e.g. pathological receptor deficiencies and excess receptors (review 1).

General Properties of Polypeptide Hormone Receptors (reviews 2, 3)

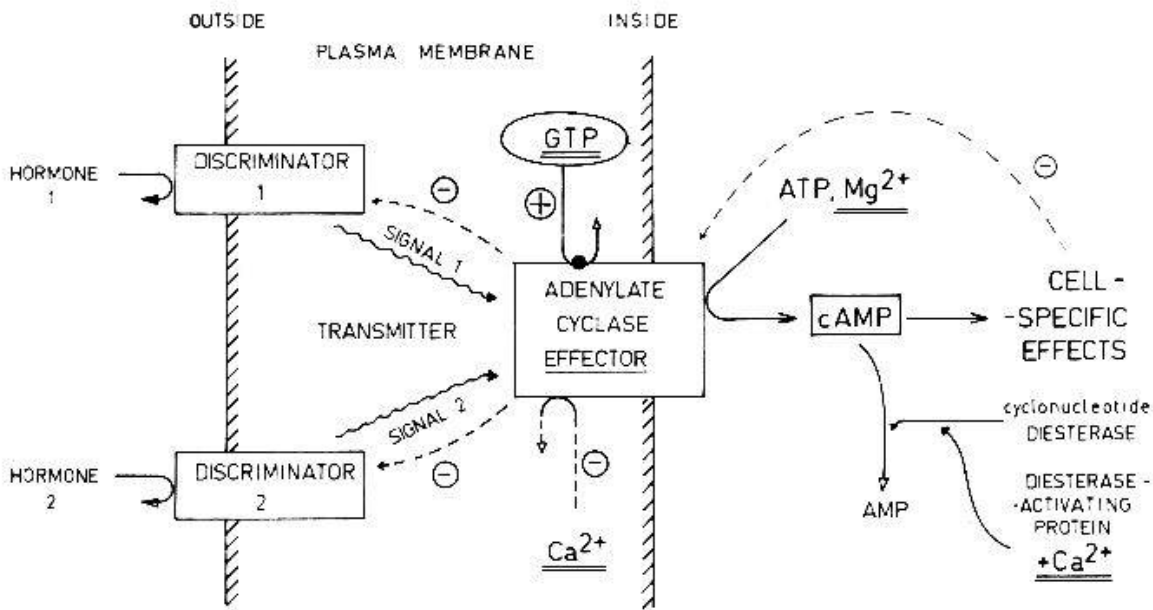
Hormones are distributed throughout the body via the blood stream and intercellular fluids. Every hormone acts upon one or a number of distinct target cells to produce cell- and hormone-specific effects. To this end, steroid hormones enter their target cells, i.e. they are physically transported through the cell plasma membrane. Certain proteins, like nerve growth factor, are also suspected to act within the cell (4). A large number of polypeptide hormones, as well as acetylcholine and the catecholamines interact reversibly with the outer surface of the cell membrane and appear not to enter the cell. Only their hormonal information is transduced and made available on the inside.

The so-called receptors responsible for this transduction are integral lipoproteins of the plasma membrane. They must fulfil at least four fundamental functions: (i) The screening of the surrounding fluids and the attraction of the correct hormone (the recognition process). (ii) The physico-chemical read-out of the hormonal information, i.e. its transformation into a signal (or stimulus) that can be transmitted through the membrane. (iii) The transmission of the signal. (iv) The conversion of the signal into a meaningful metabolic or physical response that accounts for the observable hormonal effects in the cell. The sum of these functions is called information transduction through the cell plasma membrane, because hormonal information is transduced into another form of "energy", the hormonal effect or response (5).

Adenylate cyclase holoreceptors

The complexity of the transduction process is reflected in the complexity of the chemical structures. The main elements of a (holo-) receptor capable of meeting these requirements have been detected in the β -type adenylate cyclase receptors (6, 7, 8) and are shown in Figure 1. The discriminator of the outside of the plasma membrane recognizes its specific hormone by reversible association to a hormone-discriminator complex. As a consequence of this process, a signal is generated that is transmitted to the effector, in this case, the enzyme adenylate cyclase or, synonymously, adenylyl cyclase. The nature of the transmitter remains unknown: is it only a physical contact surface between the hormone-discriminator complex and the effector, or is it a special lipid or lipoprotein structure? The effector is located on the inside surface of the membrane and is exposed towards the cytoplasm. It is activated by the signal to produce from ATP, Mh^{2+} cyclic adenosine 3',5'-phosphate (cAMP),

The Adenylate Cyclase HOLORECEPTOR (with laterally mobile subunits)



RS

Fig. 1. Features of the Adenylate Cyclase Holoceptor.

a "second messenger" that activates cell-specific phosphorylase kinases and thus a number of cell-specific hormonal effects.

In cells (e.g. adipocytes) where different hormones (e.g. epinephrine, glucagon, ACTH, etc.) are capable of stimulating adenylate cyclase, the different hormone discriminators are "coupled" to one and the same set of effectors. Recent work makes it plausible that discriminators and effectors are physically separate subunits of the holoceptor and are free to move (by a diffusion process) laterally on their respective surfaces of the membrane (9). The signal transfer would then be the result of a collision or of a more or less long-range transmission through the lipid matrix. It appears that the number of discriminators can be regulated. Phenoxazones, like actinocin, 2-amino-4,6-dimethyl-phenoxazone(3)-1,9-dicarboxylic acid, can increase their number ("discriminator reserve mobilization") in a matter of seconds or minutes (10). In some β -receptor systems, the number of discriminators is reduced by agonistic activation of the holoceptor (11). Their affinity for the hormone may also be modulated by the activation process (12).

The activation of the effector by the signal involves an enhancement of its affinity towards guanosine 5'-triphosphate. The firmly bound GTP apparently keeps the effector in the activated state, even though the signal ceases to come through. Enzymatic degradation of GTP reverts the effector to the relaxed, inactive state. The relaxation does not occur, if guanyl-

5'-yl imidodiphosphate, Gpp(NH)p, is used to replace GTP because this nucleotide is not degraded. The effector activation persists and, in the β -adrenergic system, the addition of antagonists does not cause relaxation. This can be explained by the fact that such antagonists react only with the discriminator and do not cause a "turn-off" signal to be transmitted (13). However, in the system of beef adrenal cortex cell plasma membranes, ACTH and many of its analogs are inhibitors at higher concentrations - even in the presence of Gpp(NH)p (14). There are also indications that the adenylate cyclase effector can be allosterically inhibited by Ca^{2+} , at least in a soluble partly purified preparation (15). Intracellular regulators of adenylate cyclase and/or cAMP accumulation have been found in lipocytes. It may be that the inhibition is caused by the released fatty acids (16). However, in addition, another inhibiting factor (Ca^{2+} ?), that is also released by the action of insulin, appears to be involved (17, 18).

In order to attenuate the signal produced by the "second messenger", cAMP, this cyclonucleotide is degraded by a special cyclic nucleotide diesterase which can be activated by an activator protein complex with Ca^{2+} (19).

Other holoreceptors

Insulin and acetylcholine are examples of hormones that do not exert their effects by activating adenylate cyclase holoreceptors. Acetylcholine activates an ion-gating holoreceptor. The case of insulin is still disputed: does it activate the production of GMP or perhaps influence the distribution of Ca^{2+} ?

Future receptor studies

The aim is, of course, to describe in chemical detail the mechanism of hormone action - kinetics, three-dimensional structures of the hormone, the discriminator, the hormone-discriminator complex, etc. The physical organization of receptors (as described above) poses severe problems for their isolation. Upon disruption of the lipid matrix, the functionality is lost and only the "subunits" can hopefully be isolated in a more or less functional state. Extremely difficult reconstitution studies will have to be conducted in order to prove their functional cooperation.

Failing the necessary methods for the isolation and the reassembly of the holoreceptor subunits, structure-function and structure-binding studies with polypeptide hormones and chemically altered molecules, so-called analogues, that react with receptors still located in tissues, isolated cells, or cell membrane preparations provide an indirect approach to the understanding of the transduction process besides providing insight into the organization of the

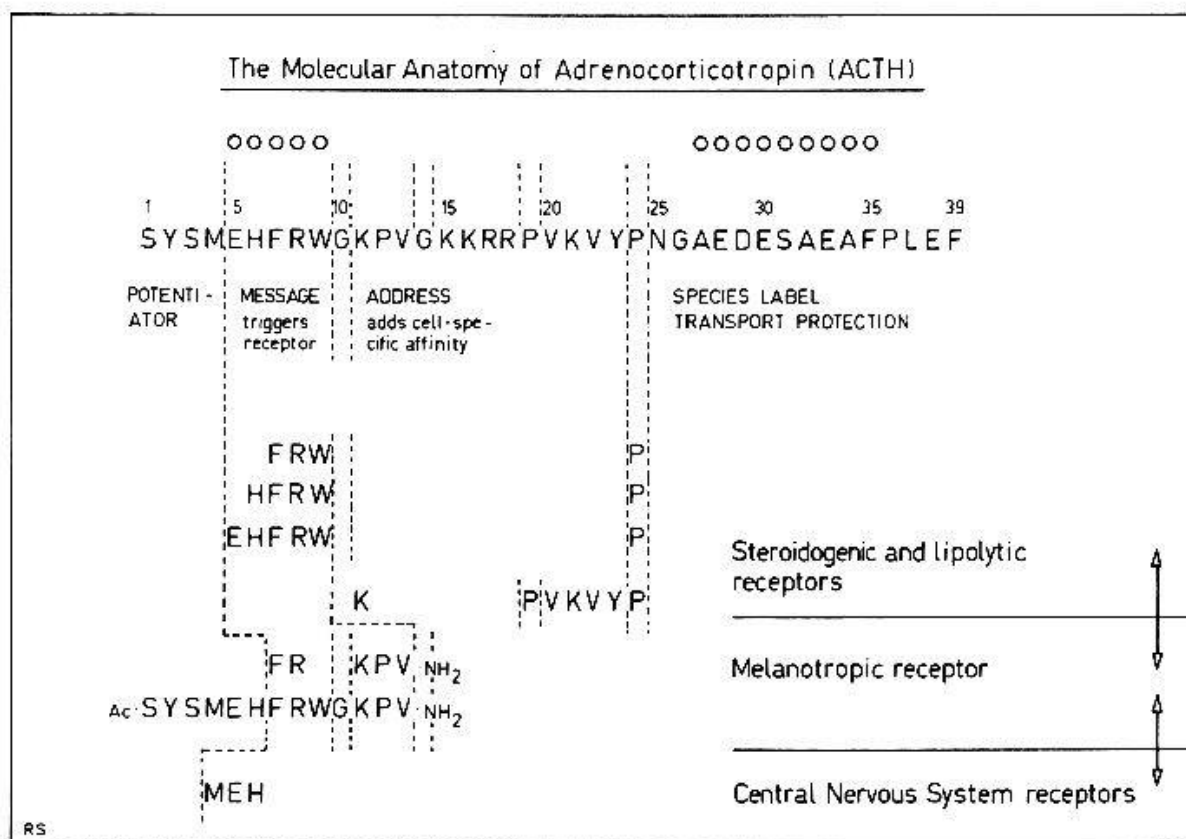


Fig. 2. The Molecular Anatomy of Adrenocorticotropin. Possible helix-forming sequences: ooo. Further explanations, see text.

hormonal information in polypeptide hormone molecules. The results of such studies in the field of adrenocorticotropin (ACTH), α - and β -melanotropin (MSH) and (partly) lipotropin have recently been reviewed (20).

The Molecular Anatomy of Adrenocorticotropin (review 20)

The molecular elements that are responsible for the biological action of ACTH can be described in terms of their one-dimensional arrangement within the polypeptide chain or in terms of their three-dimensional arrangement in contact with the (assumedly) complementary surface of the discriminator.

One-dimensional organization of ACTH information

The sequence of the 39 amino acids of ACTH (the primary structure) is well known and has been established beyond doubt by chemical synthesis. Written in the one-letter code (Figure 2), it resembles a sentence of our written language. Indeed, this "sentence" has been shown to consist of several "words" with different biological "meanings". The simplest subdivision is into a C-terminal portion containing the species label and instructions for the transport

<u>An ACTH / α-MSH Lexicon</u>	
Ac-SYSMEH	Potentiate melanotropic message
EHFRW	Trigger lipolytic receptors
FR	Trigger melanotropic receptors
FRW	Trigger adenylate cyclase receptors (adrenal / fat cells)
HFRW	Trigger adrenal steroidogenic receptors
KPV	Trigger melanotropic receptors
KPVGKKRR	Address specifically adrenal & fat cells
MEH	Trigger CNS attentiveness receptors
NGAED ELAEAFPLEF	I am of porcine origin
NGAEDESA EAFPLEF	" " " human "
NGAEDESAQA FPLEF	" " " bovine / ovine "
NSFEDESVENMGPEL	" " " dogfish "
SYSM	Potentiate steroidogenic / lipolytic / adenylate cyclase message
VKVY	Trigger α -type fat cell receptors for Mg^{2+} influx

RS

Fig. 3. An ACTH/ α -MSH Lexicon.

(in the blood stream), a central portion containing an "address" responsible for a large part of the recognition by the discriminator, a "message" which triggers the receptor, and a "potentiator" element intimately connected with the message at the N-terminus.

These three main parts of information are connected by two amino acids, glycine (10) and proline (24) that are known to add freedom of rotation and to break three-dimensional secondary structures. Recent research has shown that glycine (14) and proline (19) are further points of subdivision (like spaces between words; whether or not proline (36) is also such a spacer, remains unknown). Thus, EBERLE (21) has shown that KPV (11-13) is a message for the melanocyte MSH receptors, and ELLIOTT et al. (22) have shown that VKVY (20-23) is intimately connected with the ability of ACTH to activate the transport of Mg^{2+} into fat cells by means of a receptor with properties very similar to that of an α -adrenergic receptor (discussion of this result, see below). CNS receptors are triggered by still other portions, e.g. ME (4,5).

We have recently been able to demonstrate further, more detailed subdivisions of the classical message EHFRW (5-9). Whereas ACTH-(1-24)-tetracosapeptide (23) is a full agonist on adrenal cortex and fat cells, the peptide (RW.....P (8-24) is inactive. Addition of N-terminal phenylalanine as in FRW.....P (7-24) produces a partial agonist for membrane adenylate

cyclase activation in adrenal cortex and in fat cell membranes. This partial agonism is retained in the peptides HFRW.....P (6-24) and EHFRW.....P (5-24); only the addition of the potentiator sequence produces full agonists. However, FRWG.....P (7-24) produces neither steroidogenesis in adrenal cortex cells nor lipolysis in fat cells. HRFW-----P (6-24) produces steroidogenesis but no cAMP accumulation in adrenal cells; no lipolysis is produced by this peptide. EHFRW.....P (5-24) activates steroidogenesis and lipolysis, as well as cAMP accumulation (14, 14).

As a result of all these investigations, a rather detailed lexicon of the words composing the ACTH sentence can be compiled. The situation is indicative of an action on different receptors by virtue of different amino-acid sequences contained in the hormone molecule – an action for which the expression pleiotropic (or synchological pleiotropy) has been introduced (20, 25). Figure 3.

Three-dimensional organization of ACTH information

The work of many groups, including my own (review 20) has clearly demonstrated that ACTH is a flexible molecule in aqueous solvents. Local preferred conformations may appear in more lipophilic surroundings: they may include helical secondary structures in the regions 5-10 and 26-35 (26). In the case that a helical structure is assumed on the discriminator surfaces, then the melanocyte discriminator would be triggered by one side of the helix, the adrenal and fat cell receptors by the other (Figure 4; it must be mentioned that the amino acid sequences of ACTH and α -MSH are identical in this region). In this case the potentiator could – besides having a putative direct effect on the discriminator – exert an effect on the assumption of the correct 3-D structure by the message sequence (27). However, this point, illustrated in Figure 4, is completely speculative.

Features of Adrenocorticotropin-Activated Receptors for Adenylate Cyclase, Steroidogenesis, and Lipolysis in Adrenal cortex Cells, Fat Cells, and their Membrane Preparations.

The action of ACTH (adrenocorticotropin) on steroidogenesis in adrenal cortex cells and on lipolysis in adipocytes is believed to be mediated by cAMP (28). Indeed, the hormone causes the activation of adenylate cyclase in plasma membrane preparations and the accumulation of cAMP in isolated cells and tissues. However, cyclase activation and cAMP accumulation require hormone concentrations that are between one and two orders of magnitude greater than those eliciting the steroidogenic or lipolytic responses. This discrepancy was explained by the assumption of a large receptor reserve (29): in these special cases this means that a very small (1 %) rise of the cAMP concentration above the generally quite consider-

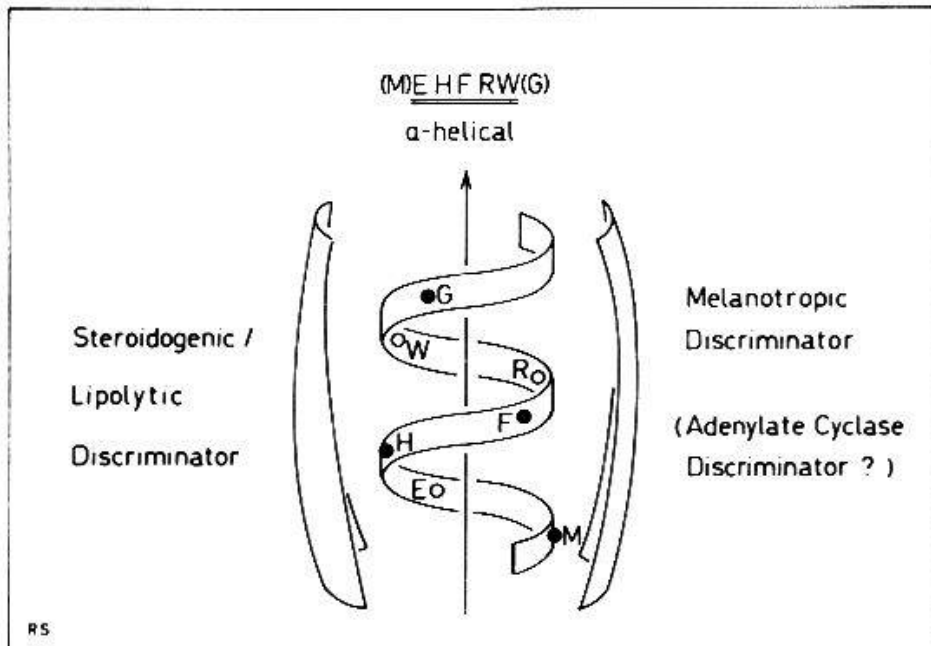


Fig. 4. A Possible Threedimensional Arrangement of the ACTH/MSH Message Sequence 4-10 as an α -Helix on the Steroidogenic/Lipolytic, the Adenylate Cyclase, and the Melanotropic Discriminators.

able background value would suffice to produce up to 30 % of the maximal steroidogenic or lipolytic responses. The sensor for such a small fluctuation is supposed to be a special "compartment" into which the newly formed cAMP is fed. cAMP production is considered both a necessary and sufficient condition for lipolysis and steroidogenesis. (Figure 5.)

The Dual Receptor Concept

Besides the single receptor - receptor reserve model presented above, a dual receptor model has also been considered (29, 30). According to it, adenylate cyclase activation and cAMP accumulation are considered to be sufficient, but unnecessary events. It assumes the presence of an additional receptor that can produce the hormonal response independently of cAMP.

The Compartment Guidance Concept

Our earlier work has led to the formulation of the compartment guidance concept for the steroidogenic and lipolytic actions of ACTH (31). This model assumes cAMP to be a necessary, but insufficient condition for eliciting steroidogenesis and lipolysis by ACTH. Besides the ACTH-activated adenylate cyclase receptor, another receptor would exist, that would guide existing cAMP into its activation of the later hormonal effects: it cannot produce steroidogenesis independently of cAMP. The second receptor has the further quality of inhi-

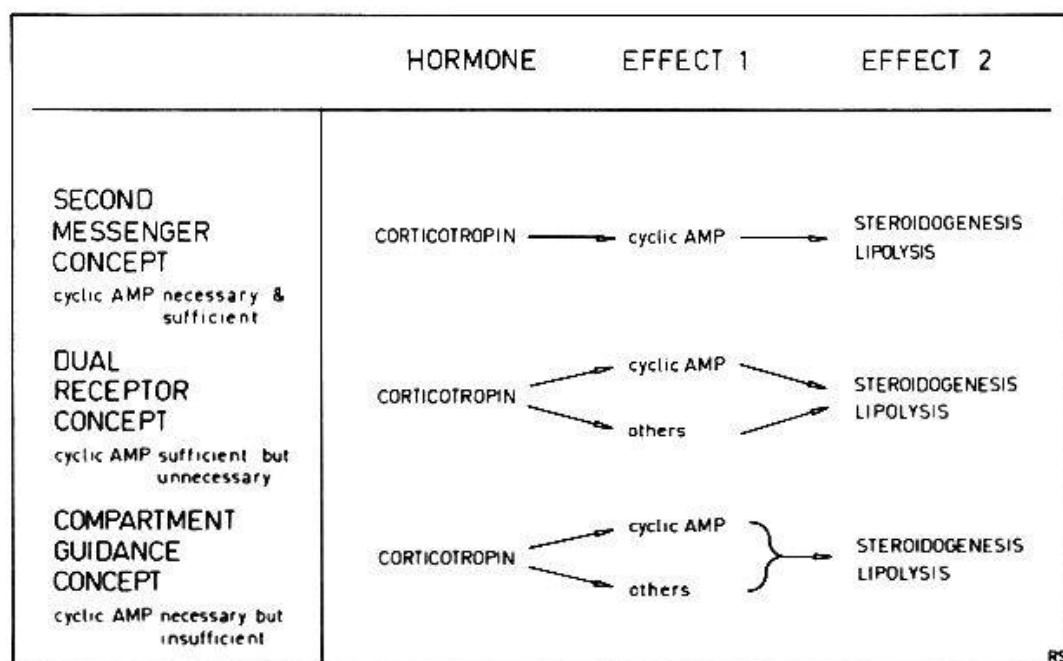


Fig. 5.

biting the action of ACTH on the adenylate cyclase receptor, and it works only in the presence of a sufficient external supply of Ca^{2+} . Adenylate cyclase activation by ACTH would be a kind of emergency effect caused by abnormally high ACTH concentrations. That cAMP is insufficient in physiological doses to produce steroidogenesis and lipolysis, but requires the action of histidine (6) and glutamic acid (5) of the ACTH molecule is, of course, supported by our experiments reported above (14, 24). It also receives strong support from observations by RUBIN (32) on the role of ACTH and calcium in cAMP production and steroid release from the isolated, perfused cat adrenal gland. The authors state (a statement that had escaped our earlier attention (31)): "These observations confirm that an increase in tissue cAMP, in the presence or absence of calcium, is not sufficient to elicit steroid release, but that an additional effect of ACTH is also required".

Comparison of the Dual Receptor (DRC) and Compartment Guidance Concepts (CGC)

The essential elements of the two concepts and of the "straight" cAMP Second Messenger Concept (SMC) are compared in Figure 5. In the CGC and SMC, cAMP is conceptually the second messenger, in the DRC it is one of two possible second messengers. The TRC and CGC are supported by work indicating two discriminator populations in adrenal cells (33): Binding experiments indicated the presence of about 3,000 sites per cell with $K_{\text{diss}} = 2.5 \times 10^{-10}$ M and 30,000 sites with $K_{\text{diss}} = 10^{-8}$ M. Only about 12 % of the total number of 33,000 sites had to be occupied in order to produce the maximal rate of steroidogenesis ($\text{ED}_{50} = 4 \cdot 10^{-10}$ M).

The dissociation constant of the low-affinity sites correspond more closely to the ED_{50} of cAMP accumulation (however, the authors discussed their results only in terms of SMC plus receptor reserve). The work of NEHER (34) which suggests that "...calcium serves as a direct messenger in the physiological activation by ACTH, cAMP being a subserving factor maintaining full steroidogenesis" fits both DRC and CGC. Another type of partial dissociation of lipolysis from cAMP production was introduced into the ACTH-adipocyte system by hyperosmolar glucose, which enhanced the effect on cAMP but reduced that on lipolysis (35). Similar dissociations of cAMP production from the hormonal effects proper have also been observed for other hormones: Bovine and porcine diabetogenic proteins produce lipolysis without increasing cAMP levels (36), indicating that lipolysis is not dependent on cAMP production (but not necessarily independent of cellular cAMP!). A study correlating human chorionic gonadotropin binding, cAMP accumulation, and testosterone production in isolated interstitial (Leydig) cells from adult rat testes indicated that a 1 % occupation of receptor sites (about 60 out of a total of 6,000 with a "uniform" $K_{diss} = 10^{-10}$ M) produces maximal steroidogenesis, but no measurable cAMP accumulation. Increasing receptor occupancy at higher hormone concentrations produced cAMP accumulation at progressively earlier time intervals, but did not alter the 20 - 30 minute time lag for testosterone synthesis (37).

Identification of the "other" receptor in DRC or CGC

The problem has not been resolved whether the ACTH amino acids histidine (6) and glutamic acid (5) (which introduce steroidogenic and lipophilic properties into the peptide (7-24) that produces only cAMP production) act on one and the same discriminator as (7-24) or on another one to produce the "guidance effect". However, there appears to be evidence for the action of ACTH not only on a (β -type?) adenylate cyclase receptor, but also on an α -type receptor: The sequence VKVY (20-23) activates transport of Mg^{2+} into adipocyte vesicles, an effect that can be mimicked by α -adrenergic agents (22). This α -type action might also be the basis of the observed reversible autoinhibition of the adenylate cyclase receptor by various peptides in the presence of Gpp(NH)p (14). A tentative hypothesis would place the "other" receptor within the family of ion-gating receptors (ACTH was actually observed to cause changes of trans-membrane potential in adrenal cells (38)); an influence on calcium (39) (besides or connected with that on Mg^{2+} ?) is certainly an attractive perspective.

Conclusion

It is certainly too early to draw conclusions about the nature of the "other" receptor system(s) besides the adenylate cyclase receptor involved in the mechanism of ACTH action. However, it appears justified at this stage to state that "another" receptor system plays a role. Thus, if β -adrenergic agonists appear to activate one receptor only, the adenylate cyclase receptor, and if acetylcholine and insulin activate "other" receptors, different from the adenylate cyclase holoreceptor, then ACTH represents a different class of hormone activating both an adenylate cyclase and "another" receptor. Whether or not these two act independently or concomitantly in the production of the hormonal effect, is not known. The situation is summarized in Figure 6.

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