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Development of hormone receptors

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Why do hormone receptors arise?

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The hormone is a signal molecule which carries a given type of information. This information is received by a cellular signal receiver (receptor) structure, which mediates it into the cell body. Thus the information embodied by the signal (hormone) molecule acquires a 'sense', which is expressed as a cellular response. In this interpretation the hormone and its receptor form a unity, since neither of them has a 'sense' in itself. The hormones or, more precisely, the cells containing them, are the foundation stones of the hormonal system. It follows that the existence of a hormonal system presupposes the existence and, naturally, the interaction, of hormones and receptors. However, the fact that the endocrine system is an issue of evolution has prompted us to revise the concept that the hormone and its receptor could have been preexisting structures: the interaction of its corner-stones is necessarily a result of evolution itself.

The evolution of recognition

The interaction between the hormone and its receptor presupposes that they mutually recognize one another. Since, in this sense, cell-hormone recognition is a fundamental phenomenon, it seems unlikely that the receptor–hormone relationship represented the initial step of cell-environment interrelationship. Recognition processes also take place at different levels intracellularly, the simplest being the mutual recognition of the two strands of double-stranded DNA, or DNA-RNA recognition (chemical recognition in vivo). A more intricate process is enzyme-substrate recognition, in which the steric structure plays a greater role, than the amino acid sequence. A still more complex, but decisively important phenomenon is the mutual recognition between intracellular compartments. The membrane-enveloped intracellular structures seek, find, attract or repel one another, and attraction results in fusion of the membrane envelopes of compartments. Intracellular membrane fusion is a deterministic phenomenon; although its precise mechanism is still obscure, there is reason to postulate that the membrane envelopes of the intracellular compartments themselves contain certain receiver and signal molecules (markers) which account for intracellular attraction or repulsion[6].

Since DNA-DNA, DNA-RNA and enzyme-substrate recognition already appear at the lowest levels of phylogenesis (in prokaryotic cells), these phenomena may well have been involved in the origin of life, whereas compartmentalization is (apart from the single-compartment structure which satisfies the criteria of the most primitive, prokaryotic cell) the exclusive property of eukaryotic cells. Intracellular compartment formation in all probability presupposed the existence of compartment-compartment recognition, to maintain the intrinsic order. Since prokaryotes are devoid of a nuclear membrane, the source of compartment formation must necessarily have been the plasma membrane. The sugar-linked plasma membrane proteins (glycoproteins) may have been responsible from the very beginning for cell-environment recognition[14, 31], and for intracellular recognition as well. The recognition capacity of the cytoplasmic membrane is also dual in present-day living beings. Receptor-mediated endocytosis (internalization) accounts for transport of the receptor-bound structures into the cell inside coated vesicles, which themselves contain structures capable of recognition, or of being recognized, thus determining the fate of the material transported inside them. It appears that, although intracellular (compartment-compartment) recognition *virtually* represents a lower level of phylo-

genesis than cell-environment recognition, it has in fact developed from the latter.

Recognition of the environment is decisive for the cell at all levels of phylogenesis. All life-conditions of the cell are furnished by its environment, which simultaneously serves as the scource of nutriment and as the sink into which the cellular degradation products are released, and contains both useful and noxious materials. From the evolutionary point of view, that cell which fails to distinguish between the advantageous and noxious qualities of the environmental molecules is doomed to deterioration and dies without producing any progeny[7]. *Only those cells which can fully adapt themselves to their environment are capable of multiplication. Cell-environment recognition is therefore a fundamental prerequisite of evolution.*

Signal receivers and signal molecules

It is known from endocrinology that cells possess certain well-defined receptor structures which are capable of interaction with given materials (hormones). The question arises whether such predetermined interaction was possible in the initial stage of evolution, which took place primarily in an aquatic environment. The answer is unequivocally no, because free water always contains a practically infinite variety of dissolved materials. The cells representing the lowest levels of phylogenesis, regardless of whether they are prokaryotic or eukaryotic, are capable of moving from one place to another which involves a change in the quality of environmental materials (signal molecules) as well. In this light the cell-membrane-associated signal receivers (receptors) cannot be interpreted as preformed, stable structures, but rather as transient patterns arising by the continuous dynamic change of the cell membrane, and 'questioning' the (given) environment. The fluid mosaic membrane, characteristically present already at the unicellular level, makes possible not only the movement of membrane proteins, but also their assembly in different configurations. In this light the dynamic receptor theory of Koch and co-workers[21], according to which different membrane patterns capable of acting as signal receivers can arise by assembly of subpatterns in the dynamically changing fluid mosaic membrane, seems to explain the mechanism of receptor formation.

This interpretation does not exclude the hypothesis that, on the other hand, environmental materials (signal molecules) are also capable of recognizing a complementary membrane pattern, and lead to its amplification if the interaction between them – mediation to the cell of the signal represented by the environmental molecule – can take place under the given conditions[2,3,5]. The intracellular (cytosolic) post-receptor mediation system operates at all levels of phylogenesis, to mention only cyclic AMP, or the Ca^2-calmodulin system[10,19,20,22,23,29,33]. Receptor formation and/or amplification in presence of the specific signal molecule has been demonstrated experimentally in unicellular model systems, and evidence has also been obtained that the selection advantage of the cells presenting the adequate receptor pattern promotes the establishment, and evolutionary amplification, of the given receptor-hormone relationship[12]. The unicellular Tetrahymena responds to primary membrane-level interaction with a foreign molecule by increased division (higher mitotic rate), which persists over many subsequent generations. The evolutionary significance of this phenomenon is the transmission of the newly acquired information to an increased number of offspring. Thus the acquired information (hormonal or signal imprinting) becomes fixed, and the second interaction with the given signal molecule accounts for a further increase in the given cellular function over as many as 500 generations[13].

At least as important as dynamic receptor formation at the unicellular level is the presence of genetically encoded stable hormone receptors, and of a pre-programmed receptor-hormone relationship, in multicellular organisms. The conditions of signal reception serve at both levels as tools of adaptation and survival of the species (individual), which carries the receiver system. One is, therefore, obliged to postulate that, from the evolutionary point of view, the stimulus for receptor formation is the presence of the signal molecule (the future hormone), and that, once established, receptor structures persist and become stabilized if their existence, and the receptor-hormone relationship which they make possible, is advantageous for the cell, or for the multicellular organism of which the cell forms part. This does not, however, exclude that once the receptor is encoded it can, at a given stage of its development, also require the presence of the hormone. This will be explained later[8].

Interrelation of hormone and hormone receptor evolution

One might conclude from the foregoing considerations that any molecule could develop into a hormone, and any hormone (signal molecule) could induce the formation of a specific receptor. However, in reality, the hormone families are relatively small in number, and relatively few materials are utilized as signal molecules[1]. It follows that certain steric structures are obviously privileged in respect of forming cellular receptors for themselves and entering into a receptor-hormone relationship. Moreover, certain molecules which have steric structures which would make them well able to act as signal molecules, are reserved for other (non-signal) functions in the living organisms. Thus it appears that only a given set of molecules is capable of the signal function. For example, certain molecules not belonging to the neuroendocrine system are also bound at the receptor level and can even evoke a cell-mediated response, but are excluded from the receptor-hormone relationship category for reasons of system theory (receptor-mediated endocytosis, transferrin, LDL receptors, etc.).

Although the foregoing considerations seem to suggest the priority of the signal molecule against the signal receiver structure, on the grounds that the presence of the former stimulates the formation of the latter, it should be noted that of the two factors the once-established receptor seems to be the more stable structure, because changes in the quality of the signal molecules hve been regularly demonstrated in the course of evolution[18,27,28]. Thus in present-day higher organisms the receptors bear a close resemblance to their primordial predecessors, whereas the signal molecules seem to have acquired their

present role in a long evolutionary process. At the same time, the present-day signal molecules are able to bind to primitive receptor structures, too. This signifies not only a certain plasticity of the receptor's binding capacity, but also a lesser alteration of hormone quality than the alteration that would be needed to exclude immunological cross-reactions between present-day and primordial configurations.

Consideration should also be given to the fact that the current classification of the signal molecules (hormones) is largely anthropocentric, or rather vertebrate-centric, inasmuch as exclusively the signal molecules existing (identified) as such in higher organisms are regarded as hormones, whereas their less-developed forms, which also occur in vertebrates, are regarded as precursors. The precursor conception may, however, often be misleading, because at lower levels of phylogenesis the so-called precursor molecule may represent a much stronger signal (for cells of that level) than the (vertebrate) hormone proper, since both parts of the receptor-hormone system are closer to the initial stage of evolution[9,11]. Thus the classification of certain molecules as hormone or hormone precursor frequently applies only at a given level of phylogenesis (or to a given organism) and expresses a given stage in the development of the system.

While the signal molecule's role and importance in receptor formation is practically an established fact, the factors accounting for the hereditary transmission of the receptor are still obscure. The unicellular organism can, with the help of its membrane, recognize and 'memorize' the foreign molecule, which thereby acquires the role of a signal molecule, but explanations of the mode of transmission of this 'memory' to the progeny generation remain hypothetical[5,7]. If the information is membrane-associated, it should dissipate in the course of serial divisions, but this is definitely not the case. Probably the membrane-associated information becomes fixed via self-assembly of the membrane proteins. This explanation seems feasible, but fails to account for the ontogenetic encoding of the receptor, unless a gene-level fixing of some form of the membrane-associated information is postulated. However, this cannot be reconciled with the current genetic conceptions, for it implies the hereditary transmission of an acquired property. It is expected that advances in research into immunological memory[16,24] and membrane DNA[17,32] will also throw more light on the receptor 'memory' problem.

At all events, in the light of the new interpretation of the hormone and precursor categories, the gene-level fixing of receptor 'memory' seems to be the prerequisite of those mutations which account for the existing differences between the present-day and primordial receptor structures, and thereby for the greater binding affinitiy shown by mammalian receptors to the mammalian hormones than to the 'precursors' of these.

After binding the ligand, the membrane receptors become internalized, and after internalization, they are recycled to the membrane again[34]. This mechanism makes possible the degradation of the ligand, and thereby the termination of its action. Thus internalization of the membrane receptor seems to be the ontogenetic recurrence of the phylogenetic internalization process[4], which ultimately led to the formation of intracellular membrane structures (compartments). This hypothesis leads to further speculations, for, according to present knowledge, hormone receptors occur in two locations: membrane-associated, and cytosolic. Recent experimental observations have increasingly suggested, in contrast to earlier conceptions, that any hormone is capable of binding to both types of receptors, e.g. steroids can bind to membrane receptors and polypeptide hormones to cytosolic receptors[15,25,26,30,35,36]. Since, logically, all materials interacting with the cell come into contact first and foremost with its membrane, it might well be postulated that at the beginning of evolution exclusively membrane receptors existed, which gained access into the body of the cell only at a later stage, probably in a dissolved form, and gave rise therein to cytosolic receptors. Thus, although evidence is lacking, theoretically the cytosolic receptors can be regarded as descendants of the membrane receptors, which arose from the necessity of refining the mechanisms of hormone binding and hormone transport[4].

Conclusions

In view of the foregoing considerations, it appears that the receptor-hormone relationship is, by origin, essentially a cell-environment (chemical) relationship which influences cell behavior. With the development of multicellularity, the interests of the single (individual) cell became subordinated to those of the cell population (community), and the cell-environment relationship became modified inasmuch as receptor activity became integrated into the functional program of the entire organism. Accordingly, the 'open program' of the individual cell, which involved continuous dynamic changes of the membrane receptors under the influence of the signal molecules, was superseded by a 'closed program' for the given receptor, which gave rise to a chemical memory of the cell. With multicellularity the cellular functions have become integrated into an almost entirely predetermined program in which the quality and operation of the receptors are encoded to maintain the system of regulation, and impart differentiating features to given types of target cells which distinguish them from others, and delimit the response potentials of the species. A limited openness of the pre-programed system exists in the early stage of ontogenesis, and accounts for certain individual variations within the limited potentials of the species.

The answer to the question posed in the title of this paper is therefore the following: the hormone receptors arise because the external environment of the individual cell is transformed at the multicellular level to an internal environment, in which the random variety of environmental molecules is replaced by a predetermined set of ligands (signal molecules). Under these conditions the randomly-presented membrane patterns capable of signal reception are transformed to encoded receptor structures which execute a programed function of the closed system, but nevertheless preserve some primordial traits, which can explain many surprising observations in the field of receptor physiology.

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Mechanisms of receptor-mediated transmembrane signalling

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Key words. Receptor; ion channels; acceptors; protein kinase; second messengers; receptor dynamics, internalization.

Receptors, acceptors, channels and the problem of transmembrane signalling

Fundamental to the successful function of any multicellular organism is an efficient communication system that can convey information from one cell to another. Although the overall function of the cell membrane is to maintain an effective barrier between the intracellular and extracellular milieu, highly specialized membrane structures (e.g. ion channels, nutrient transporters, histocompatability determinants) can be singled out as playing particularly pivotal roles in terms of selectively transmitting information from the external to the internal cell environment (and in some cases, vice versa). Over the