Outline Studies in Biology

# Cellular Recognition

M. F. Greaves

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# Contents

# 1 Biological communication and recognition

## 1.1 Signal coding

The genetic code embodies structural and functional potentiality and in differentiated cells the DNA can be compared to a punch tape that is programmed to delineate the cell's specialized activity. In order for this specific potential to be expressed in tune with the dynamic demands of the cell's environment, the biochemical pathways from gene to performance must be in contact with, and receptive to, *extracellular signals*.

This relationship exists at several levels; the integrity of an individual animal, plant or micro-organism within its total environment and the effective function of component parts all depend upon multiple regulatory controls or signals which govern and integrate the behaviour of cells, tissues, organs and individuals. Thus, while the performance potential of any given part is predetermined, the expression of this intrinsic programme is integrated into, and largely subservient to, the needs of the whole organism and occasionally the species. We may casually accept this as a fairly obvious truism today, and perhaps fail to appreciate Claud Bernard's unique conceptual and experimental insights into this problem over 100 years ago [1].

The analogy is frequently made between cells and people, both being members of heterogeneous and complex yet integrated societies. The cancer cell can then be portrayed as the wayward rebel who is unresponsive to the 'normal' conventions of society. This altruistic principle is indeed relevant to different levels of biological organization and although in practice possibly too impersonal and impractical for man, it is not apparently so for other 'social' creatures, such as bees, ants, and termites. It is, however, interesting and not altogether unexpected to find that social behaviour of these insects, like that of cells, may be a result of dictatorship rather than true altruism. [2]

Biological and machine-based transactions both involve regulated activity, which in cybernetic terms popularized by Norbert Wiener [3] are dependent upon information transfer and feedback control. Cause/effect and supply/demand are continually cross-checked and performance thereby evaluated and geared to meet the challenge. In order to understand how this is achieved, we must concern ourselves with both the structure and language of the intercellular communication systems.

The relevant structures are systems within systems (the Russian doll principle) and can be arranged into domains of descending size that are concerned with the receipt of information (i.e. stimuli), and its transmission and translation (i.e. into response).

The messages we receive from the outside world can be in the form or modality of sound, smell, visible and invisible (ultraviolet, infrared) light, heat, pressure; however, *all* are translated, via the externally orientated sensory receptors of the body, into the *common language* of the nervous system – the nerve

impulse. The language used is 'common' in the sense that it embodies no specific instructional information content. The informational significance of nerve cell communication from the sensory organs to the brain lies in the selective activity of sensory receptors themselves and the precision and patterning of the physical connections and pathways that exist. This is no explanation of how nerve impulses can be interpreted by the brain as one of a thousand different shapes or smells, or how such specific sensory brain centres and sensory organs become connected; however, it serves to emphasize that communication is via a language which by its *rate* of transmission – rather than specific content – relates *presence* and *level* of a particular stimulus and by its contacts and circuitry communicates form or quality. The reality of this arrangement is illustrated by the capacity of light, electricity and pressure to elicit a common sensation of 'light' and of the ability of judiciously applied electric pulses or catecholamines to elicit complex motor activities. So effective is direct stimulation of the 'pleasure areas' of the brain that rats are prepared to drive themselves to neural ecstasy and eventual death!

The brain is the communication headquarters and oversees virtually all vital processes in higher organisms. It communicates indirectly with tissues of the body via the pituitary gland – the neural-hormonal coupling centre – or more directly via nerve fibres. The nerve impulse itself serves primarily to regulate the release from the nerve endings of pre-packaged *chemical messages* – neurotransmitters – or 'local hormones' whose specificity of action lies in the cellular relationship served by the nerve and the possession by the 'target' cell of appropriate 'discriminatory' binding sites analogous to the body's sensory organs. Numerous important interactions exist between other differentiated cells of the body of which those mediated by hormones are the best

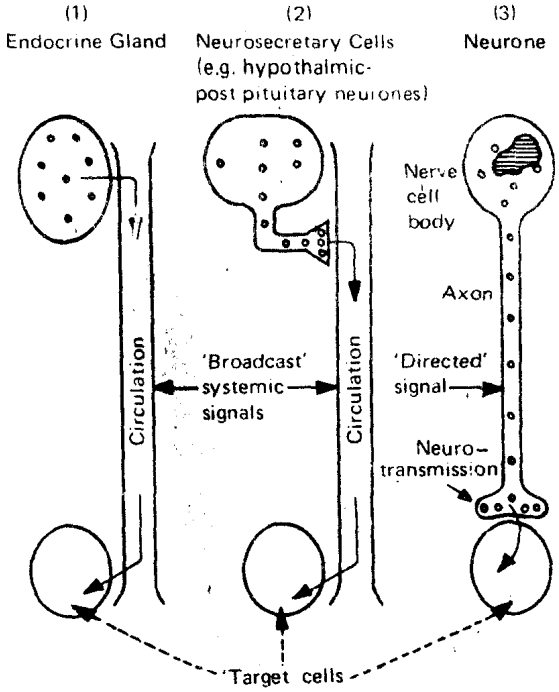


Fig. 1.1 Systemic and local 'hormones'

known and most important example. Hormones and neurotransmitters have essentially similar regulatory functions as exemplified (see Fig. 1.1) by the dual (local or systemic) role of some catecholamines ( – epinephrine) and the existence of neuro-secretory cells [4].

The languages used for *inter*cellular communication are essentially all chemical and it is undoubtedly the great diversification and sophistication of this type of signal that characterizes 'internal' biological control. Diffusible chemical signals may have a zone of influence as small as a hundred angstroms (e.g. the neuro-muscular junction) or throughout the whole organism (blood-borne messages such as hormones) or extracorporeally, over a few kilometres (given a favourable wind!)

Chemical languages vary in their vocabulary and correspondingly in their specificity – 'depending on the privacy of the messages

delivered and the intricacy of the transaction being proposed' [5]. They exist for inter and intra-species' communication as odours (or pheromones) which are usually, although not invariably, volatile [6], for intercellular relay both as soluble diffusable neurotransmitter substances and hormones, and as cell surface associated molecules. Intracellular chemical messages exist in the form of cyclic nucleotides (see Chapter 4) and the primary message exists encoded in the base sequences of nucleic acid.

All communications of importance in regulating biological activity involve multiple parameters often with sequential changes of language. The way in which these signals are integrated and interpreted however, at present eludes us. It is a common human experience that smells evoke salivation, whereas to a male moth, miniscule amounts of female odour can induce vigorous flight upwind in hot pursuit of sex. We are far from understanding the nature of odour discrimination, however, we can appreciate that in each example a sensory device for distinguishing between different chemicals has converted or translated this modality of information into the common language of nerve excitation and via various relays, back again into an internal chemical signal responsible for eliciting the overt physical response of salivary glands or wing muscles.

Consider also a person, not altogether uncommon, who introspects and communicates to others solely in the English language. Samuel Pepys' cyphered diaries are lost on him, as is a message in bush telegraph, smoke signal, morse, pictoglyphics, semaphore, hieroglyphics, shorthand or Portuguese. Input information is 'received' but not understood. In this sense all versatile information signalling systems are encoded in *arbitrary* units (phonemes to linguists), and are by no means the sole prerogative of 'spies'. Signals then have no intrinsic 'meaning' and their significance lies in the association they involve and the responses they elicit. Arbitrary encoding has obvious advantages:

(1) It enables as few as two units, by combination or patterning, to represent complex messages (i.e. the computer binary code).

(2) It assures privacy by reserving interpretability only to those intimate with the codes.

(3) It greatly increases the efficacy of communication over relatively large distances without loss of privacy (e.g. Napoleon's heliograph in Egypt and Nelson's semaphore at Trafalgar).

Regulatory signals in biological systems are elicitive rather than instructive (i.e. 'Darwinian' rather than 'Lamarkian'). Indeed, it could hardly be arranged otherwise, since the basic instructions for response are in the recipient's genes. The key to an understanding of the way cells 'talk' to each other lies not only in the physicochemistry of the signals themselves, but also in the means by which they are deciphered.

### 1.2 Signals and the cell surface

We now know that the receipt and translation of signals is largely a cell surface phenomenon and is dependent upon the existence of membrane associated 'cognitive' elements or *receptors*. In many cases, these have been directly identified and partially or completely purified, in other systems their existence is entirely hypothetical. Steroid hormones provide an important exception to this generalization. In this case, the specific receptors are intracellular and the efficacy of the steroid signal, therefore, depends crucially on its lipophilic (hydrophobic) nature which enables it to enter cells [7].

The cell surface membrane is a two-dimensional interface between a cell and its immediate extracellular environment and as such, provides the ideal venue and physical platform for interactions and signal reception. Besides maintaining the general physical and

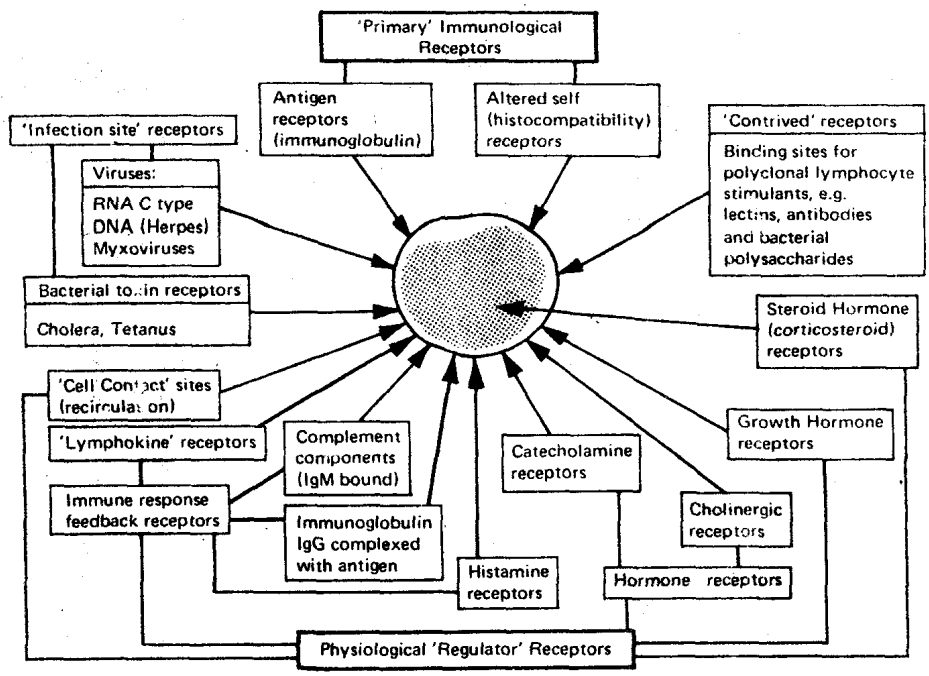


Fig. 1.2 The sensory world of lymphocytes

metabolic integrity of the cell, the surface membrane therefore serves as an elaborate sensory device capable of detecting environmental signals which induce, alter, or regulate cellular activity. Multiple receptor types can be identified on individual specialized cells, and a parallel with sensory organs of the body surface is suggested by the finding that separate receptors for different chemical signals may co-exist on the same cell and communicate intracellularly using a common chemical language. Thus, in fat cells, hepatocytes and other cell types, receptors for several different hormones exist on the cell surface and the activity of each appears to be associated with the activation of adenyl cyclase [8]. This enzyme in turn catalyses the formation of cyclic AMP – a ubiquitous small molecule which has become known as the 'second messenger'; the first messenger being the hormone or other ligand impinging upon the cell surface (see below). Functionally differentiated or specialized cells each have their own particular spectrum of surface receptors which delineate the diversity of potential environmental signals and the accessibility of the cell's performance to regulation. Fig. 1.2 illustrates a speculative but plausible view of the sensory world of lymphocytes. No two specialized cells and no two species of micro-organism or animal have the same sensory capacity – to plagiarize Von Uexkull [9] they each have their own 'Merkwelt' (perceptual world).

The way in which the cell membrane performs its function of signal recognition is not understood and represents one of the great challenges of present-day biology. The simple conceptual framework shown in Fig. 1.3 illustrates the principles likely to be involved (see also [10]).

The first component involved, is the cognitive element or receptor which functions

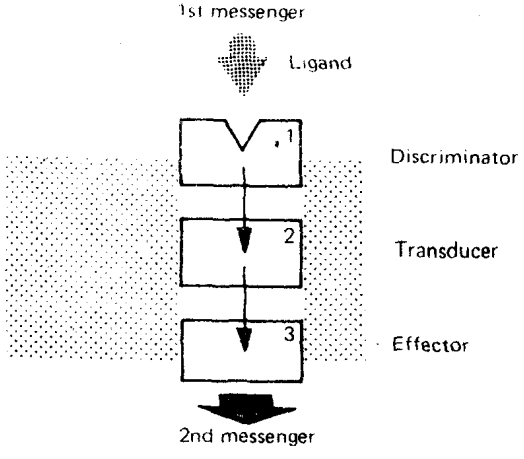


**Fig. 1.3** A model for receptor function in cell membranes (largely based on [10]).

as a *discriminator* for detecting a particular specific regulatory signal, whether this be a soluble ligand or a component of another cell surface. Two key features of receptors are therefore their asymmetric cell surface disposition and their combining site specificity, since they govern input and the range of regulatory signals which can feed into the system. From recent concepts on membrane structure it seems that outward orientation of the active binding site(s) on a receptor may be guaranteed on thermodynamic grounds, provided it is associated with hydrophilic or polar regions of the molecule. Its specificity will depend upon its more detailed chemistry as will be described below.

Receptors, however, serve for the selective receipt of signals *and* for the initiation of the cellular response. In a general sense, therefore, without prejudice as to their nature, we can consider them as bifunctional molecules, with the crucial quality of being able to communicate ligand binding to the *transducer*. The transducer is the most illusive element in the chain and in some respects the most vital, since it has the responsibility of translating the binding activity of the receptor into the appropriate second signal. In principle, therefore, this component has a signal-response coupling function analogous to the electromagnet in many man-made communication devices. It may be part of the receptor molecule itself or a separate molecular entity (see Chapters 4 and 5).

The third vital element in information transfer across membranes is the 'effector', 'transmitter' or 'amplifier' component which is responsible for communicating altered cell surface activity into the interior of the cell. In many recognition systems (e.g. many polypeptide hormones and catecholamine neurotransmitters) this component is almost certainly the enzyme, adenyl cyclase. In other systems other plasma membrane enzymes (e.g. guanyl cyclase, Na, K dependent ATPase) or ion gating molecules may serve an equivalent effector role (see Chapter 4).

Whilst the structural *diversity* of receptors is predictable from specialization of cell function and the variety of regulatory signals, there is no *a priori* reason why transduction and effector mechanisms in cell membranes should be greatly diversified. On the contrary, it is to be expected that different cell types would employ a few common mechanisms which reflect some general properties inherent to membrane structure and function and which are to be found in phylogenetically primitive beasts. Indeed, the integrative function of biological membranes must have been a prerequisite for the diversification of cell function.

The 'second messenger' has already been identified in a great variety of cell response systems as cyclic AMP [11]. Recent evidence suggests that cyclic GMP may have an essentially similar messenger role, although one which is often antagonistic to cyclic AMP [12]. These two intracellular signals are regulated at the membrane-cytoplasm interface by inward orientated cyclase enzymes (Fig. 1.3). It is possible that a few other (but not many)

analogous 'messenger' molecules exist and in principle at least these could be derived also from outside the responsive cell – their uptake being stimulated as a result of transducer activity. We should perhaps also bear in mind that receptor activity frequently results in 'turn-off' (or step down) rather than 'turn-on' (or step up) regulatory activity and, in principle at least, stimulation could result from the *reduction* of an *inhibitory* signal. It can be anticipated that these general principles may also hold true for those receptor components of the body's sense organs which are involved in the transduction of external sensory input (of various modalities) into nerve impulses. I should not be surprised if the crucial membrane events involved in neurotransmission at cholinergic synapses in the human nervous system are very similar to those occurring in the pheromone receptors of insects or even in the chemoreceptors of bacteria and protozoa. Such a situation might be anticipated on simple theoretical grounds since the receptor cells of many sense organs are embryologically part of the nervous system [13]. The analogy is further supported by recent data which suggests that cyclic nucleotides may play an important role in visual processes in the retina [14].

The biochemical identification of these three elements in membrane recognition (discriminator, transducer, and transmitter), and the resolution of the way in which they exercise their concerted function provides one of the most exciting and important pursuits of biology.

Recent basic developments in concepts of membrane structure and function (see Chapter 3) leave little doubt that an understanding of receptor function requires an integrated analysis of rapid sequential changes in the activity of mobile components of an essentially fluid cell surface membrane. This poses the classical dilemma of 'integrationist' versus 'reductionist' approaches. Obviously, receptors must be isolated and their chemistry unravelled. However, their function only has significance and finds expression in terms of dynamic associations between receptor molecules and other membrane constituents. To paraphrase Francois Jacob [15] – membrane recognition events may be explained by the properties of the components but cannot be deduced from them.

The nature of this problem is such that interdisciplinary research is mandatory and it is gratifying to find that the cell surface is already a common meeting ground for probing biochemists, biophysicists, embryologists, immunologists, pharmacologists, and the like.

The significance of the problem can be brought home by reference to the systems to which it applies. Cellular recognition phenomena are both diverse and fundamental in living systems. They encompass sexual unions (i.e. sperm-egg in metazoan animals, pollen-stigma in flowering plants, mating types in bacteria, algae, fungi and protozoa), the development of specialized and stereotyped contact relationships in embryogenesis (particularly those involving the nervous system), the interaction of cells with neurotransmitter and hormonal signals, interaction of cells with viruses, symbionts, parasites and antigens, and finally and most formidably, the integrative functioning of the brain. Some of us believe, perhaps somewhat optimistically, that cellular recognition via the surface membrane holds the key not only to understanding the complexities of development, but also of cancer and other major human diseases.

It would be a prime example of 'Lavosier's fallacy'* to imagine that any one of these holds the key to all others, or that all cellular interactions must necessarily involve highly discriminating receptors. Nevertheless, a view of the cell surface as a transducer of intercellular signals has emerged and entrenched itself as a fundamental biological principle.

*This term was coined by Hartley apropos Lavosier's claim that all acids must contain oxygen.