A long engagement

Rod Flower

"To most modern pharmacologists," de Jongh wrote in 1964, "the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered these letters. From these answers the pharmacologist has built himself an image of this fair lady."

Although he was writing almost 20 years before the first detailed structural account of any receptor, at a time when our knowledge of receptor mechanisms was slight, this concept had already spawned many outstanding pharmaceutical innovations. One thinks, for example, of the development of beta-blockers and of selective histamine antagonists. So how did this most influential idea come about?

The notion that drugs act through receptors has its true origins in the late nineteenth century, when dogma held that the cell protoplasm is a single, very large, molecule. Paul Ehrlich introduced the term 'receptor' in 1900 to describe sites on this molecule to which bacterial toxins (and, later, drugs) bind to bring about changes in cellular metabolism. The idea of discrete and specific binding sites was also supported by the experiments of John Newport Langley. His observations on the antagonistic actions of curare and nicotine on skeletal muscle eventually led to the key concept that drugs possess two properties: the ability to bind to the 'receptive substance' (as he called it) or affinity; and the ability of an agonist to cause an effect, later dubbed its efficacy. The final impetus came from Alfred Joseph Clark, who realized that the relationship between drug concentration and response could be described using a simple mathematical model, and who thus bequeathed us the rudiments of receptor theory.

By the late 1940s, the balance of evidence and opinion had swung towards the Ehrlich–Langley–Clark model of drug action, and in the ensuing years it was to become as close to a credo as science allows. These early pioneers had laid the foundations of experimental pharmacology and had ensured that even if its practitioners did not know what receptors actually were, they at least had the conceptual tools to work with them.

Originally, the term 'receptor' was applied generically to all drug targets because there was no clear sense of how binding gives rise to a biological effect. Some of these targets subsequently turned out to be enzymes or other molecules, and today the term 'receptor' is generally reserved for a molecule that acts as a biological signal transducer — usually for endogenous hormones or neurotransmitters.

Like the omnipresent mobile phone, a receptor must not only be able to pick out the correct signal from the blizzard of irrelevant traffic, but also cause it to be amplified and converted into a form that is useful to the recipient. Clearly, a mere docking molecule cannot accomplish such a feat. Langley, showing more than a little prescience, believed that the receptive substance "is capable of affecting the metabolism of the chief substance" (by which he meant the secretory, contractile or other apparatus) of the cell. A breakthrough in understanding how this could occur came with the discovery of signal-transduction systems — biochemical relays that link receptor occupation to the phosphorylation of key proteins, changes in calcium or accumulation of 'second-messenger' molecules that ultimately modify such cellular processes. Research into these phenomena has become a distinct discipline in its own right.

From the genome sequences of humans and other organisms, we now know that there are thousands of different cellular receptors. But we have also come to appreciate how thrifty nature has been in limiting their basic molecular design, providing just a handful of 'superfamilies'. The most abundant of these is the highly conserved seven-transmembrane-domain G-protein-coupled receptor, a design so adaptable that these receptors can be modified to detect 'ligands' as diverse as photons of light or the most complex polypeptide hormones. The opportunities for rational drug design on the basis of these similarities between members of superfamilies are not being overlooked.

But despite these tremendous advances, many questions remain. The nuances of drug action *in vivo*, structural data and predictions based on mathematical models can sometimes be irritatingly difficult to reconcile. Other disturbing facts have surfaced too — some receptors lack any signalling properties, whereas others seem to have their ligands already attached. Flouting conventional receptor theory, some drugs seem to behave both as antagonists and as agonists, depending on how they are administered; and (embarrassingly) even the fundamental idea of efficacy has been difficult to measure — or even to define. It seems that after 100 years of acquaintance and 50 of intellectual matrimony, our relationship with de Jongh's "mysterious lady" is still not fully consummated. Perhaps we should have insisted on a prenuptial agreement! ■

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Drug receptors

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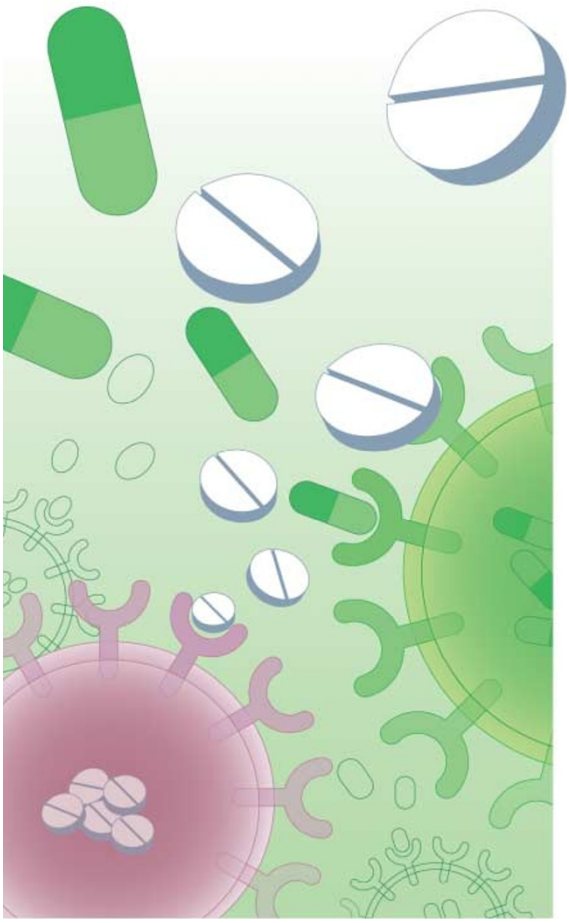

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FURTHER READING

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