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Physiological Receptors are macromolecular protein complexes that serve as recognition sites for neurotransmitter and hormones. The term receptor, however, is also widely used to refer to any component of a cell that can bind a drug, which then modulates some activity of the cell. Thus, in addition to the regulatory proteins (enzyme, ion channels, carrier molecules and neurotransmitter and hormone receptors), any other component of the cell may act as a receptor for a drug. An example would be the antimicrobial agent, ciprofloxacin, which binds to a DNA gyrase and inhibits the super-coiling of bacterial DNA.

Receptors therefore lie at the very heart of neuroscience and, of course, they are a keystone concept in pharmacology and other biomedical science disciplines. The original concept of the receptor was introduced independently at the end of the 19th century by John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915).

Langley (Figure 1) was educated at home, Exeter Grammar School and Cambridge University, where he obtained his degree in Natural Sciences in 1874 and where he remained throughout his academic career. Langley is best known for his work on the physiology of the Autonomic Nervous System (ANS) and on gland secretion (1). Whilst still an undergraduate and at the suggestion of his mentor Dr (later Sir) Michael Foster, the first Professor of Physiology in Cambridge, Langley began a study of the action of Jaborandi (pilocarpine) on the mammalian heart. Langley's experiments not only showed that pilocarpine slows the heart rate but also "that a definite quantity of atropia [(atropine) could] prevent a proportionate definite quantity of jaborandi from producing its effects on the heart" (2).
In subsequent experiments Langley also used the drug to explore salivary secretion and showed that pilocarpine could induce secretion from the salivary gland (in the cat and other experimental animals) and that this effect could be stopped by atropine. With increased amounts of pilocarpine the antagonist actions of atropine could be reversed. Langley recognized the parallels with the antagonistic action between Jaborandi and atropine on the heart that he had demonstrated earlier and considered the mechanism of the interaction between these two poisons and the cell. In 1876, with remarkable insight, Langley suggested that "there is some substance or substances in the nerve endings or gland cells with which atropin and pilocarpin are capable of forming compounds. On this assumption then the atropin or pilocarpin compounds are formed according to some law of which their relative mass and chemical affinity for the substances are factors. In the analogous case with inorganic substances, other things being equal, these are the sole factors" (3).

From the 1880s, Langley worked on the anatomical and functional properties of the ANS and utilized other drugs, including nicotine and curare, as tools of investigation. In the course of these investigations, a critical question addressed by Langley was the site of action of nicotine on skeletal muscle cells. In 1905, Langley had shown that nicotine was able to induce its characteristic tonic contraction of skeletal muscles in anaesthetized fowl, even when the nerves to the limb had been cut and allowed to degenerate. This result indicated that nicotine acted directly on the muscle cells rather than paralysing the motor nerve ending, as had been suggested from the work of Claude Bernard in the 1840s and 1850s. By injecting curare, the nicotine-evoked contraction was abolished, an effect that clearly paralleled the antagonism between pilocarpine and atropine Langley had described some 27 years earlier. He concluded that either curare compounds or nicotine compounds were formed with the muscle cell, depending on the relative amounts of the two poisons. However, even after administration of curare, Langley had also discovered that the muscle was able to contract in response to direct electrical stimulation of the muscle. From these observations, Langley drew the critical conclusion that nicotine (and curare) did not act directly on the muscle but rather on some accessory substance of the muscle cell. "Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the receptive substance of the muscle" (4).

Paul Ehrlich (Figure 2) is best known for his work on immunity for which he was awarded the Nobel Prize for Medicine/Physiology in 1908, the development of selective chemotherapeutic agents, especially against syphilis and the foundation of haematology through his use of new dye staining techniques. He was born to a middle-class family in Strehlen, Silesia, then part of south-eastern Germany and now a part of Poland. He was sent to the St Maria Magdalena Humanistic Gymnasium in Breslau where he excelled in Latin, mathematics and the sciences, especially chemistry and biology. Ehrlich entered the University of Breslau to study medicine in 1872. However, because a student could transfer from one institution to another, Ehrlich was also able to study at the
Universities of Strasbourg and Freiburg before presenting his thesis and taking his degree at the University of Leipzig in 1878 (5).

Figure 2: Paul Ehrlich.

Ehrlich's MD thesis addressed the selective histological staining of cells and tissues using numerous dyestuffs. In his voluminous thesis, Ehrlich proposed that the reactions between aniline dyes and cells was a chemical rather than a physical interaction, that there was a specificity between the dye and the cell or tissue it stains, and further that the chemical structure of the dye molecule defined its solubility and ability to attach (bind) to cells. As others have noted (4), here was the seed of a receptor theory. From these studies, Paul Ehrlich laid the basis for understanding the relationship between the chemical structure of aniline dyes and their differential staining abilities. It is also noteworthy that, at 24 years of age, Ehrlich also reported in his thesis the discovery and naming of the mast cell.

In subsequent experimental studies, undertaken between 1878 and 1888 at the famous Charité Hospital in Berlin, Ehrlich further investigated the use of stains in relation to clinical medicine. Amongst many important discoveries, Paul Ehrlich identified eosinophils, neutrophils and basophils and undertook fundamental studies on the identification of the anaemias and leukaemia. These findings were of critical importance for histology and the establishment of the new discipline of haematology. For his habilitationsschrift (1885), a thesis required for appointment as a university lecturer, Ehrlich again undertook ground-breaking research and introduced the use of redox dyes to address the oxygen-fixing capacities of various tissue cells in the body. Significantly, Ehrlich speculated that the oxygen was fixed to cells by binding it to certain side chains of the cell.

Following a break from work due to pulmonary tuberculosis (possibly contracted in the laboratory) and a trip to Italy and Egypt with his wife, Hedwig, Ehrlich joined Robert Koch in 1890 at the Moabit Hospital in Berlin. In 1891, in the newly established Institute for Infectious Diseases in Berlin, Ehrlich began to address the interactions between toxins such as tubercle bacillus and antitoxins or antibodies formed in the blood. During the 1890s, Ehrlich conducted many important pioneering immunological studies (and for them was awarded the Nobel Prize in 1908) and significantly established the method for the production and standardization of high potency antitoxin sera products. In 1897, to explain the process of immunization, Ehrlich proposed his side-chain theory, by which certain "side-chains" of the cell were able to bind certain toxins. Because these occupied side-chains would then become unable to fulfil their physiological functions, the cell would over-compensate by producing additional side-chains. These side-chains would then be released into the blood stream, where they acted as antitoxins or antibodies (6). By 1899, Ehrlich was appointed Director of The Royal Prussian Institute for Experimental Therapy located in Frankurt-am-Main and where he remained until his death 16 years later.

By 1900, Ehrlich had begun further pioneering studies in chemotherapy and famously developed
the first specific anti-syphilis drug, *Salvarsan*, in 1906. To explain the *selective toxicity* of 
*Salvarsan* and other chemotherapeutic agents (such as the trypan red dye against trypanosomes) 
but not closely related compounds, Ehrlich extended his side chain theory to include side chains or 
*chemoreceptors* for drugs – a modification, Ehrlich later acknowledged, in part due to the brilliant 
investigations by Langley on the effects of alkaloids.

From these pioneering experimental studies undertaken independently by Langley and Ehrlich the 
concept of receptors emerged. Subsequent quantitative analysis of drug action on cells by A. J. 
Clark in the 1930s provided receptor occupancy theory, later modified by E. J. Ariens (1954) and 
R. P. Stephenson (1956) to account for drug efficacy and spare receptors. R. P. Alquist's 
investigations of the actions of adrenaline (epinephrine) and related drugs gave rise to the now 
famous proposal of alpha and beta adrenoreceptor subtypes in 1948. Together these ideas led Sir 
James Black to develop receptor subtype selective drugs and, in particular, the first clinically 
useful beta-blockers in the mid-1960s. For his work Black was awarded the Nobel Prize for 
Medicine/Physiology in 1988. By the early 1980s, the nicotinic acetylcholine receptor had been 
isolated, purified, its subunit stoichiometry determined and cDNA sequences for its subunits 
reported. In 1994, Alfred G. Gilman and Martin Rodbell were awarded the Nobel Prize in 
Medicine/Physiology for their work on the discovery of the G-protein receptors and their role in 
signal transduction (6).

Today, we recognize a large and growing number of physiological receptors that can be delineated 
in to at least four *receptor super-families* on the basis of their distribution, function, 
pharmacology and molecular biological properties. These receptor super-families, namely the 
*channel-linked* receptors, *G-protein-coupled* receptors, *enzyme-linked* receptors and *intracellular* 
receptors are the focus of a multi-national, multi-billion dollar pharmaceutical industry. A primary 
aim of this industry is to develop *magic bullets* – a selective drug to treat a specific clinical 
condition without side effects – an idea proposed 100 years ago by the German Physician and 
biochemist, Paul Ehrlich.

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**Acknowledgements**
A Wellcome Trust History of Medicine grant to Prof A-H Maehle and Dr R. F. Halliwell is supporting this work on the History of Receptors. The author is grateful to Dr Roger Carpenter, The Physiological Laboratory, Cambridge University for permission to use the photograph of John Newport Langley.

Some nice quotations referring to receptors

"I may perhaps take the liberty of inviting you to look into the workshop of the chemotherapist. The whole field is governed by a simple, I might even say, natural, principle. If the law is true in chemistry that corpora non agunt nisi liquida [substances are active only in solution], then for chemotherapy the principle is true that corpora non agunt nisi fixata [substances do not act unless bound]."


"To most of the modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly claim ever to have seen her, although one day he may do so."


"Although some progress has been made in the isolation of receptors & their characterization in chemical & physicochemical terms, for most part receptors must be regarded as hypothetical entities, even though the receptor concept lies at the heart of pharmacology."