TIMELINE

The emergence of the drug receptor theory

Andreas-Holger Maehle, Cay-Rüdiger Prüll and Robert F. Halliwell

Today, the concept of specific receptors for drugs and transmitters lies at the very heart of pharmacology. Less than one hundred years ago, this novel idea met with considerable resistance in the scientific community. To mark the 150th anniversary of the birth of John Newport Langley, one of the founders of the receptor concept, we highlight his most important observations, and those of Paul Ehrlich and Alfred Joseph Clark, who similarly helped to establish the receptor theory of drug action.

Until the second half of the nineteenth century, the remarkable potency and specificity of the actions of drugs such as morphine, quinine and digitalis were explained vaguely and with reference to extraordinary chemical powers and affinities to certain organs or tissues[1–3]. Only from the 1860s was the relationship between the chemical structure of a drug and its pharmacological action studied systematically[4,5]. Today, it is a basic tenet of pharmacology that most drugs act by binding to specific macromolecules (receptors), either in or on cells, to change their biochemical or biophysical activity and thus their cellular function. This short historical review considers the origins and early development of the idea of the 'drug receptor', a concept that has become increasingly important in biomedical sciences in general, and in pharmaceutical sciences in particular, over the past century.

As historians of pharmacology, such as John Parascandola[6] and Günther Stille[3], have pointed out, although the idea of drug receptors was clearly formulated as early as the first decade of the twentieth century, there was a long delay in its scientific acceptance and practical application. This article explores the question of why this delay occurred. We argue that the development of the receptor concept depended to a large extent on the scientific predilections of its early protagonists and, for a long period, encountered resistance from the scientific community. In the first part of this article, we highlight how the two founders of the concept, the Cambridge physiologist John Newport Langley (1852–1925) and the Berlin immunologist Paul Ehrlich (1854–1915), arrived at their conclusions over the period 1870–1910 . Second, we draw attention to the objections to their receptor theories, and to alternative ideas on drug action in the first three decades of the twentieth century. Third, we close with some remarks on how the theory of receptors was strengthened through the new quantitative approach to the study of drug action on cells that was developed by the Edinburgh pharmacologist Alfred Joseph Clark (1885–1941) in the early 1930s.

The conception of the receptor theory

Langley (FIG. 1) is perhaps best remembered for his experimental work on the autonomic nervous system and on glandular secretion[7]. In fact, his ideas on receptors emerged from both these areas. At the suggestion of his mentor, the eminent Cambridge physiologist Sir Michael Foster (1836–1907)[8], Langley's first published research, in the mid-1870s, concerned the physiological action of the drug jaborandi and its newly isolated alkaloid, pilocarpine[9–11]. In experiments on the salivary gland of the cat, Langley showed a mutual antagonism between pilocarpine and atropine. This led to his first reflections on the nature of drug binding to cells. He assumed that atropine or pilocarpine combined with the cell by forming compounds in the way that two inorganic chemical substances combine with each other. Whether atropine compounds or pilocarpine compounds prevailed depended on the chemical affinity of the alkaloid for the cell, and on its concentration at the site of action[12]. However, after these remarkable early insights, Langley was drawn for the next 15 years into the details of research on glandular secretion[13].

From the late 1880s, Langley developed a new focus for his research. He turned to functional analysis of the autonomic nervous system using nicotine poisoning as a tool[14,15]. For a long time, however, it was controversial whether alkaloids such as nicotine, pilocarpine and atropine, and hormones such as adrenaline, bound directly to effector cells — that is, to gland cells or muscle cells — or to the nerve endings that terminate on these cells. On the basis of experiments that were undertaken in the 1840s and 1850s by the French physiologist Claude Bernard (1813–1878), it was still widely held that curare acted primarily to paralyse the peripheral endings of motor nerves in the muscle[16,17].

In 1905, against this background, Langley examined the effect of nicotine on muscles in which nerves had been cut and allowed to degenerate. The animal model that was used in these trials was the anaesthetized fowl, in which injection of nicotine produces a characteristic tonic contraction of certain muscles of the leg. This contraction could also be induced in the denervated leg muscle, which indicated that nicotine might act directly on the muscle cells. By injecting curare into the animal, the contraction could be abolished. Langley realized that this was a parallel case to the antagonism between pilocarpine and atropine that he had described 27 years earlier. He concluded that either curare compounds or nicotine compounds were formed with the

muscle cells, depending on the concentration of each poison. However, even after administering curare, direct electrical stimulation of the muscle could still produce a contraction. From this observation, Langley drew the critical conclusion that the poisons did not act directly on the contractile substance, but rather on some accessory substance of the muscle cell. Because this accessory substance was conceived to be the recipient of chemical or nervous stimuli (which it transferred to the contractile material), Langley called it the 'receptive substance'. Using the language of chemistry, he speculated that these substances were radicals of the large 'protoplasmic molecule'. With acknowledgement to Ehrlich, he called them 'side-chain molecules'[16,18].

Langley's path to the receptor concept shows that it was not the product of a systematic research plan, but rather developed, intermittently, over 30 years in response to questions that arose in the course of his experimental work. The receptor concept was a by-product of Langley's physiological research into the autonomic nervous system.

Paul Ehrlich (FIG. 2) was the first researcher to develop an elaborate theory around the receptor idea. This was the outcome of several factors, including certain aspects of his socialization in the German university system. In particular, as a Jew, it was initially difficult for Ehrlich to secure a tenured position[19]. Indeed, he succeeded in becoming Director of his own institute in Berlin only because of the supporting influence of Robert Koch (1843–1910) and his research group[20], and help from the Prussian Ministry of Science[21]. As a result of these events, Ehrlich's research became largely theoretical.

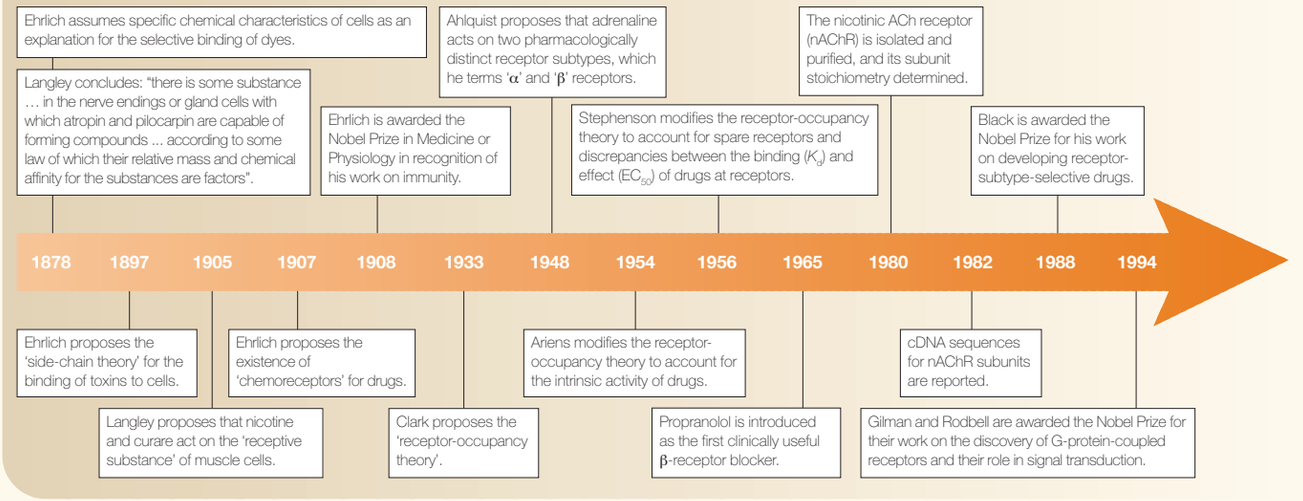
Ehrlich's main interest was the application of chemistry, and especially of staining procedures, to medical problems. In his M.D. dissertation in 1878, he speculated that there must be a specific chemical character of the cell that is responsible for the selective binding of dyes[22]. The actual development of the idea of side chains entered into Ehrlich's clinical work in Berlin between 1878 and 1888, when he investigated the cellular use of oxygen. For Ehrlich, the dyes indicated the affinities of the various tissues for oxygen, and he speculated that the cell used oxygen by attaching it to certain side chains of the protoplasmic molecule[23]. However, such theorizing had no major role in Ehrlich's daily clinical work.

It was only after a break in Ehrlich's career, because of the death of his clinical teacher Theodor Frerichs (1819–1885), that Ehrlich returned to his ideas on side chains. He felt compelled to resign from his clinical position in 1888. This meant that he could no longer combine clinical work with laboratory research, and he therefore concentrated increasingly on the latter as the focus of his studies. Ehrlich was now inspired by the bacteriological research of Koch and Emil von Behring (1854–1917). He turned to immunological problems, especially to the interactions between bacterial toxins and antitoxins or antibodies, which are formed in the blood[24]. It was only in 1897 that he developed a full 'side-chain theory' of the toxins. Certain side chains of the cell could bind certain toxins. Because these occupied side chains would then be unable to fulfil their physiological functions, the cell would over-compensate by producing further side chains. These side chains would then be released into the bloodstream, where they would act as antitoxins or antibodies[25].

Ehrlich's new immunological interests were clearly driven, in part, by his need to establish an independent scientific laboratory, and to place his scientific career on a safe footing. Owing to the influence of Friedrich Althoff (1839–1908) — the Ministry Councillor in the Prussian Ministry of Science — Ehrlich became head of his own institute in Berlin in 1896, and, then, in 1899, in Frankfurt (Main)[21]. The side-chain theory became the core of further work in immunology. Ehrlich postulated the existence of many side chains, and, in 1900, he introduced the term 'receptor' as a replacement for the term 'side chain'[26]. During this period, Ehrlich addressed the structure and classification of receptors and postulated the existence of multiple receptor types with different numbers of binding groups. These included 'amboceptors' (FIG. 3), 'triceptors', 'quadriceptors' and even 'polyceptors'[27,28]. This concept was highly speculative, but Ehrlich was drawn more and more into the 'pluralism' (Ehrlich used the term *Plurimismus*) of his receptor world[29]. His detailed research led to a complex system of numerous interacting immunological substances. This work also opened the path for studies on metabolism in the human body in general.

As with Langley, Ehrlich's receptor concept was not developed from a primary interest in drugs or drug actions, but rather was the outcome of his engagement in various other research projects. In addition, his interests were partly determined by the changing and complex external circumstances of his academic career.

Timeline | **Key events in the discovery and establishment of the concept of receptors**



Critics of the receptor concept

Both Langley and Ehrlich encountered immediate criticism of their receptor concepts. Ehrlich's toxin–antitoxin ideas were challenged by Elie Metschnikoff's (1845–1916) ideas on the phagocytosis of bacteria[30]. Jules Bordet (1870–1961) launched an attack on the pluralistic character of Ehrlich's immunological theory and questioned the existence of a variety of immune bodies[31]. The Munich Professor of Hygiene, Max von Gruber (1853–1927), also criticized the pluralistic view of Ehrlich, emphasizing the high degree of speculation in Ehrlich's work[32].

When Langley presented his concept of receptive substances at the International Congress of Physiologists in Heidelberg in 1907 (REF. 33), he was confronted with a critical paper by the Heidelberg pharmacologist Rudolf Magnus (1873–1927). Magnus argued that trials with antagonistic poisons said nothing about their site of action[34]. In this way, he discounted one of the arguments in favour of Langley's receptor concept; namely, the antagonism of nicotine and curare on the denervated muscle. Two years later, the Cambridge pharmacologists Walter E. Dixon (1870–1931) and Philipp Hamill (1883–1959) critically examined both Langley's and Ehrlich's receptor ideas. Experimenting with the alkaloid strychnine, and with emulsions of spinal cord, they found no evidence for a chemical combination of the alkaloid with the nervous tissue. Accordingly, they questioned the existence of specific receptors for alkaloids[35]. Further criticism of the receptor concept followed in 1910 from Henry Hallett Dale (1875–1968), who then worked in the Wellcome Physiological Research Laboratories. Together with the chemist George Barger (1878–1939), he found that a wide range of amines of different chemical structure apparently mimicked the effects of sympathetic nerve stimulation. Because Barger and Dale could not identify a structural component that was specific for these sympathomimetic substances, they rejected Langley's notion of a chemical union between receptive side chain and drug[36].

Despite these criticisms, neither Ehrlich nor Langley gave up their receptor ideas. On the contrary, Ehrlich accepted Langley's point that receptors existed not only for toxins but also for drugs. In 1907, on the basis of his experiments with dyes on trypanosomes, Ehrlich assumed the existence of 'chemoreceptors'[37]. In the years until his untimely death in 1915, Ehrlich used the receptor concept in this sense in the development of his chemotherapy for syphilis[38]. In addition, Langley provided new experimental evidence for two types of nicotine receptor in the frog muscle — one leading to twitching and the other to tonic contraction[39,40] — and, in 1921, in his monograph on the autonomic nervous system, he speculated on two broad classes of receptive substances: "… those which give rise to contraction, and those which give rise to inhibition"[41].

Nevertheless, pharmacologists did not readily adopt the receptor theory. During the period between 1895 and 1930, at least four main alternative theories of drug action were considered. These were the physical theory, the physicochemical theory, the Arndt–Schulz Law and the Weber–Fechner Law. The physical theory emphasized the surface tension of the cell membrane, which influenced the concentration gradient between the inside and outside of the cell, and, consequently, the effect of the drug on the respective organ[42]. The physicochemical theory combined the physical point of view with the chemical assumptions of Ehrlich and Langley[43]. The Arndt–Schulz Law postulated that: "Weak stimuli excite, medium stimuli partially inhibit and strong stimuli produce complete inhibition". This theory was influenced mainly by homeopathic thinking and flourished, especially in the 1920s in Germany, when scientific medicine was criticized on the basis of ideas about individual human constitution and the influence of the environment on human health[44]. The Weber–Fechner Law proposed that there is a constant relationship between dose increment and the effect of a drug. It suggested that the effect of the drug followed the logarithm of its concentration. This idea was a component of a more general law, which had been proposed in psychology to explain the discrimination of sensory stimuli in humans[45].

Most important was the physical theory of drug action and, in particular, the contribution of the Freiburg pharmacologist Walther Straub (1874–1944). He was a pupil of two main protagonists of experimental pharmacology, Rudolf Boehm (1844–1926) in Leipzig, and Oswald Schmiedeberg (1838–1921) in Strasbourg[46]. Straub became one of the most prominent pharmacologists internationally. Particularly relevant were his 1905 experiments with muscarine on the isolated heart of the sea snail *Aplysia*. Muscarine causes a decrease or complete cessation of the heart rate. Straub concluded from his experiments that this effect depended on absorption of the alkaloid into the muscle cell. He believed that it did not depend on the effect of the poison inside the cell itself. Rather, the decisive factor was the difference in the poison concentration between the outside and the inside of the cell. Straub called this the 'concentration potential'. These observations were the basis of his so-called 'potential-poison theory'. He speculated that while the poison was entering the cell through the membrane, the membrane became unable to excrete the chemical waste products of the cell. This damaged the cell, and eventually brought its functions to a standstill. Straub thought that his potential-poison theory would also be applicable to other alkaloids, such as pilocarpine, physostigmine and nicotine, as well as to the hormone adrenaline[47].

In 1912, Straub gave a lecture to the Society of German Natural Scientists and Doctors about the importance of the cell membrane in pharmacological action. In this lecture, he stated that a general theory of chemical binding between drugs and cells, as Ehrlich had imagined, was "going too far" and was "not admissible" and also "not fruitful". For example, several biologically active substances, such as nitrous oxide and carbonic acid, which were thought to be chemically inert, would not, therefore, react chemically with molecules of the cell. Straub admitted, however, that there might be chemoreceptors for certain poisons, but thought this was an insufficient basis for building a whole theory of receptors[48].

A new synthesis — A. J. Clark

By the early 1930s, significant support for the concept of drug receptors emerged from the quantitative analysis of drug action on cells by Alfred Joseph Clark (1885–1941). In 1933, Clark published his book *The Mode of Action of Drugs on Cells*, in which he collated, analysed or re-analysed data from a large number of diverse pharmacological studies, including his own. Clark recognized that — as one of the youngest biological disciplines — pharmacology had been largely concerned with the qualitative nature of drug effects. In his view, recent advances in chemotherapy and therapeutics had led to a need to establish the quantitative relationships of drug actions (Clark was also fiercely critical of the 'quacks' who pedalled fraudulent medicines for which there was little, or no, scientific evidence)[49]. From these beliefs, Clark sought to discover what laws of 'physical chemistry' might be "… postulated regarding the combination formed between drugs and cells"[50].

From calculations of molecular size and cell surface area, Clark realized that drugs, such as adrenaline and acetylcholine, at the low concentrations needed for their biological effects, were unlikely to form a monomolecular layer over heart cells. Rather, such drugs were likely to "… exert their action by uniting with certain specific receptors in or on the heart cells"[50]. Clark thought that these receptors formed only an insignificant proportion of the total surface of the cells.

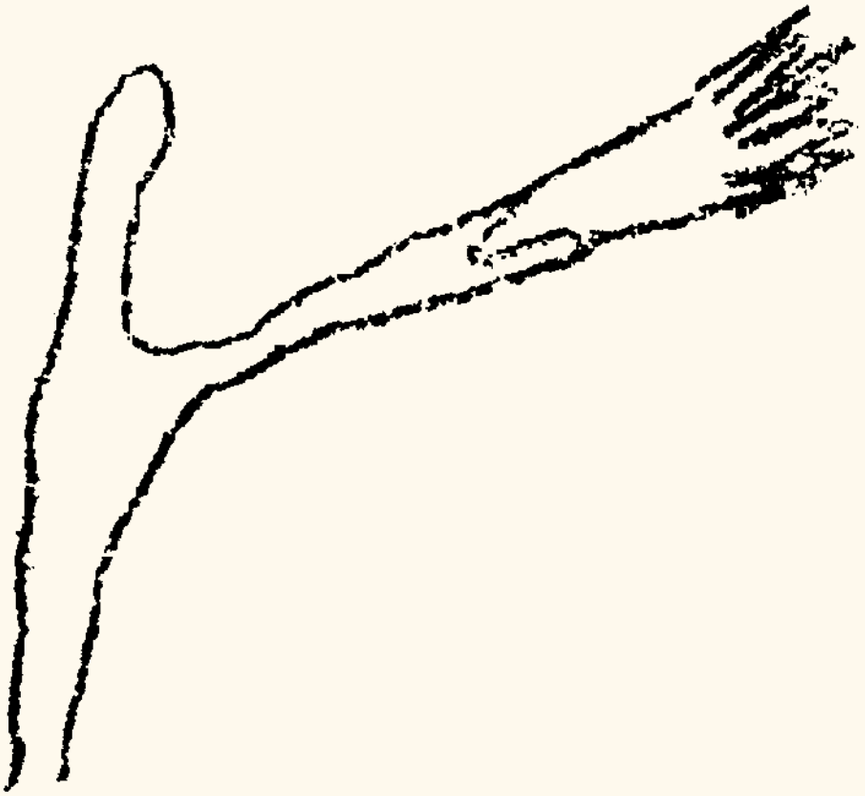


Figure 3 | **The amboceptor.** A substance (on the right) is bound to one of the two binding sites of the side chain. Hitherto unpublished sketch by Paul Ehrlich, 1901. Courtesy of the Rockefeller Archive Center, New York.

His mathematical approach also recognized that the Law of Mass Action (modelled by the Hill–Langmuir equation) probably governed the rate of adsorption (binding) of drugs to cells, and that — for many drugs — the relationship between drug concentration and biological effect followed a simple hyperbolic function. A parallel example was known in physical chemistry: the adsorption of a gas onto a metal surface also followed a simple hyperbolic relation. This relationship expressed the simplest form of adsorption, in which one molecule of a gas united reversibly with one receptor on the surface. Clark concluded that the hyperbolic curve of drug action expressed the equilibrium between a drug present in excess that reacts with a finite number of cell receptors to form an easily dissociable compound. He concluded further that the pharmacological action that was produced was "directly proportional to the number of receptors occupied"[50]. Modifications to this receptor-occupancy theory — by E. J. Ariens (Utrecht) in 1954 and by R. P. Stephenson (Edinburgh) in 1956 — to account for the intrinsic activity (efficacy) of a drug (that is, its ability to induce an effect after binding) and the recognition of spare receptors, now form the basis of pharmacodynamic analysis[51].

Conclusions

The development of the receptor concept between the 1870s and the beginning of the Second World War was not a continuous and focused effort. The research of Ehrlich and Langley left a lasting mark on the history of pharmacology, but it was not until Raymond P. Ahlquist (1914–1983) made his famous distinction, in 1948, between α- and β-adrenoceptors[52] , that receptor research began to provide a powerful basis for pharmaceutical innovation. In the period that we have reviewed, the receptor concept was used in Ehrlich's chemotherapy, but it remained highly speculative, and was in strong competition with other theories of drug action. In particular, the potential-poison theory of Walther Straub could have been a significant obstacle to an earlier recognition of the concept of receptors. The receptor idea emerged only slowly and intermittently from diverse research fields. It arose, in particular, from work on the physiology of the nervous system, early chemical work on metabolism, the beginnings of immunology and, later, from a mathematical analysis of pharmacological data. In the past 20 years, work in molecular biology has provided the genetic basis for the concept of receptors and, furthermore, has supported and even extended the pharmacological evidence for the great diversity of receptive substances[51]. Interestingly, these more recent data also present a new challenge — to incorporate genetic information into the classification schemes of diverse receptor families.

The early pioneers of the receptor concept, notably Langley and Ehrlich, and later Clark, clearly recognized the importance of receptors in understanding diverse biological phenomena and, with great insight, they also anticipated its potential for pharmacotherapy.

Andreas-Holger Maehle and Cay-Rüdiger Prüll are at the Centre for History of Medicine and Disease, Wolfson Research Institute, University of Durham, Queen's Campus, Stockton, University Boulevard, Stockton-on-Tees TS17 6BH, UK.

Robert F. Halliwell is at the Department of Physiology and Pharmacology, T. J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, California 95211, USA.

Correspondence to R.F.H.
e-mail: rhalliwell@uop.edu

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