

ESSAYS ON APS CLASSIC PAPERS |

Alpha- and beta-adrenergic receptors: Ahlquist's landmark hypothesis of a single mediator with two receptors

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This essay looks at the historical significance of an APS classic paper that is freely available online:

Ahlquist RP. A study of adrenotropic receptors. *Am J Physiol* 153: 586–600, 1948 (<http://ajplegacy.physiology.org/cgi/reprint/153/3/586>).

FOR THOSE INTERESTED in the areas of autonomic physiology and adrenergic pharmacology, there is perhaps no paper more important than Raymond Ahlquist's (Fig. 1) seminal contribution in the *American Journal of Physiology* in 1948 (3). This paper established two fundamental concepts: first, that a single sympathetic mediator could produce both excitatory and inhibitory responses; and second, that adrenergic receptors were of two different types based on rank order potency of activation by agonists. To appreciate the importance of this remarkable paper, three pieces of background information are helpful.

First, around 1900 John Jacob Abel successfully isolated epinephrine in relatively pure form (2). Starting in the 1920s, W. B. Cannon attempted to identify the chemical transmitter of the sympathetic nervous system (which he called sympathin), and in 1933 he mistakenly concluded that there were two sympathins, sympathin E (excitatory) and sympathin I (inhibitory) (7). This was due, in part, to the fact that he was using a natural preparation, adrenalin, which at that time was a variable mixture of epinephrine and (up to 35%) norepinephrine.

Second, Dale's classical work (8) on the influence of ergot alkaloid antagonists on the effects of epinephrine and sympathetic nerve stimulation suggested two distinct types of receptors for epinephrine. One type, through which epinephrine produced excitatory responses, was "paralyzed" (blocked) by ergot alkaloids, whereas the other type, through which epinephrine mediated inhibitory responses, was not paralyzed by ergots.

Third, in 1948, Ahlquist defined the "adrenotropic" (now known as adrenergic) receptors as "those hypothetical structures . . . affected by epinephrine" (3). Ahlquist further noted that "the adrenotropic receptors have been considered to be of two classes, those whose action results in excitation and those whose action results in inhibition of the effector cells," and these in turn were assumed to be activated by sympathin E and sympathin I, respectively.

Against this backdrop Ahlquist chose to investigate the actions of six closely related catecholamines on multiple func-

tions in multiple species (dogs, cats, rats, and rabbits). The drugs used were arterenol (norepinephrine), cobefrine (α -methylnorepinephrine), epinephrine (both racemic and levo), methyl-epi (α -methylepinephrine), and *N*-isopropylarterenol (isoproterenol). Responses were investigated in both intact animals and isolated tissue preparations, including contraction and relaxation of various vascular and uterine smooth muscles, dilation of the pupil, and stimulation of myocardial contraction. He found, for example, that "the relative order of activity of these amines as myocardial stimulants . . . [was the] same as that found for their vasodilator actions. This indicates that the myocardial receptor is related to the vasodilator receptor rather than to the vasoconstrictor receptor." In fact, with perhaps one exception, the rank orders of catecholamine potency for all tissues and functions fell into one of two distinct patterns. Based on these observations, Ahlquist insightfully concluded that these adrenotropic effects, regardless of being excitatory or inhibitory, were mediated by two distinct receptors; "tentatively the first kind of receptor has been called the alpha adrenotropic receptor and the second kind the beta receptor."

Ahlquist's critical new concept was that receptor types/subtypes should be defined by their pharmacological characteristics, i.e., the rank order of drug potencies, rather than by

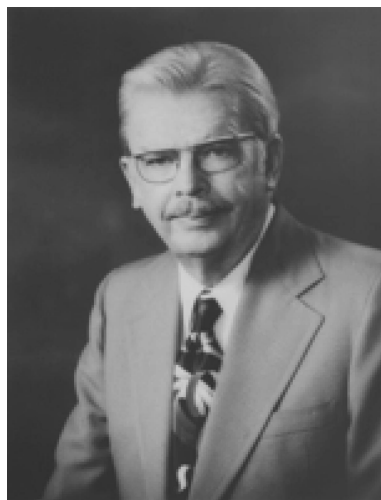


Fig. 1. R. P. Ahlquist. Courtesy of National Library of Medicine.

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the nature of their physiological response. His classification scheme was supported by the fact that responses mediated through α -receptors could be blocked by the ergot alkaloids, whereas responses mediated through β -receptors could not. In addition, as he noted in his paper, "This concept of two fundamental types of receptors is directly opposed to the concept of two mediator substances (sympathin E and sympathin I)...now widely quoted as a 'law' of physiology." The similarity to the parasympathetic system did not escape him: for "the cholinergic nerves there has never been any suggestion that there might be two mediators, although both excitatory and inhibitory effects are produced. The diverse effects of the cholinergic mediator, acetylcholine, have always been ascribed to differences in the receptors upon which it acts." Thus he concluded, "Use of the terms sympathin E and I should be discouraged. . ."

Looking back some years later, Ahlquist made two noteworthy comments on this paper that are illustrative of how science is really done. First, he noted that their studies were not designed to classify adrenergic receptors, but that his discovery "was the byproduct of a research effort to find a drug that would relax the myometrium when this structure was contracted by vasopressin" (5). He also observed that they were continuing their studies, and had "results that, unfortunately, can be interpreted" in several ways. "However, since experimental design, deliberate or unconscious, can produce results that will support almost any theory it is obvious that we will favor our previous ideas" (4). This is of course fine, as long as your previous ideas are in fact correct.

As might be expected, Ahlquist's classification scheme was not immediately accepted. In 1959, Furchgott (9) reviewed the data for the α and β classification compared with a scheme with "excitatory," "inhibitory," and "undifferentiated" adrenergic receptors as suggested by Lands (11); thus even 11 years after the original publication, Ahlquist's proposal was not yet well accepted. In fact, Ahlquist himself viewed a receptor as a "concept," rather than an "entity": "Although a receptor is a very useful concept to describe drug actions, tissue responses and structure-activity relationships, it should be kept in mind that invoking a receptor mechanism does not explain the real nature of the interaction between a tissue and a drug. When better knowledge of a receptor is obtained, for example, the exact identification of the enzyme or enzyme system involved, the need for the receptor vanishes. . . Although the alpha and beta receptors have achieved international usage it should be stressed that they have only interim value until the exact nature of the responsive mechanism for adrenergic agonists is discovered" (5).

In response to the question of why Ahlquist's proposal encountered so much resistance, Sir James Black has suggested that it was because the term receptor was widely used at that time in a very general sense (pressure receptors, sensory receptors, chemoreceptors, etc.). "The only people who talked about receptors as interactive entities was a small cadre of pharmacologists who were interested in the quantitative relationship between dose and response. . . a pure idea, necessary to allow them to do the math. But they were embarrassed about it, that it was a pure invention. . . And so when Ahlquist claims to find two receptor types—that stuck in everybody's throat. His was the first explanatory use of the term 'receptor'" (1).

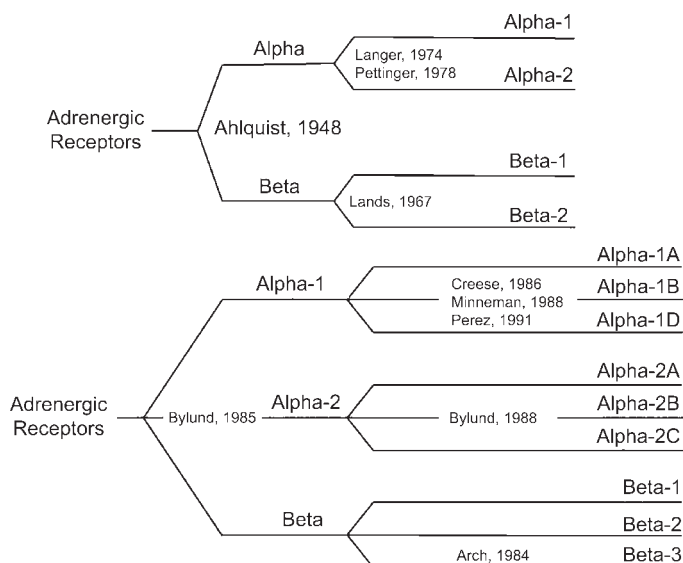


Fig. 2. The original (top) and current (bottom) classifications of adrenergic receptors, emphasizing the early and prominent role of Ahlquist's 1948 paper (3). The references for the other papers noted in the figure can be found in Ref. 6.

However, Ahlquist's concept of α - and β -receptors, as well as of classifying types and subtypes of receptors by their pharmacological characteristics, has stood the test of time and has served science extremely well. Adrenergic receptors were subsequently further classified into various types and subtypes as is shown in Fig. 2, which includes the current classification scheme of three types each with three subtypes. Two aspects of this scheme deserve emphasis. First, the classification of adrenergic receptors (in particular, and many other families of receptors in general) by pharmacological (rank order of drug potency) and molecular (primary amino acid sequence) criteria agree remarkably well, although there is no a priori reason that this should necessarily be the case. This is also true for other receptor families. Second, of the nine adrenergic receptor subtypes, eight were defined pharmacologically, just as Ahlquist did, before they were defined molecularly (the one exception being the α_{1D} subtype).

The International Union of Basic and Clinical Pharmacology (IUPHAR) currently provides the definitive classification of the various receptors (10). Receptors are divided into four superfamilies, one of which is the seven transmembrane (or G protein-coupled) receptors. Within this superfamily are 61 families, including the adrenergic receptor family, defined by the presumed endogenous neurotransmitter/hormone. Within those 61 families there are now some 175 types/subtypes of receptors (<http://www.iuphar-db.org/>), again defined largely on the basis of the rank order potencies of agonists and antagonist—clear proof of Ahlquist's remarkable insight on how to best classify receptor subtypes.

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