CC/NUMBER 47
NOVEMBER 23, 1981

This Week's Citation Classic

Lands A M, Arnold A, McAuliff J P, Ludaena F P & Brown T G, Jr.

Differentiation of receptor systems activated by sympathomimetic amines.
Nature **214:597-8,** 1967.
[Sterling-Winthrop Research Institute, Rensselaer, NY]

On the basis of the relative agonist activities of norepinephrine and certain norepinephrine analogs, catechol ethanol amines in all instances, in selected autonomic systems, data have been presented to show that an a-, β–,β2-adrenoceptor delineation is in better accord with experimental findings than can be encompassed within an a- and β-receptor one initially proposed. [The *SCI*® indicates that this paper has been cited **over** 875 times since 1967.]

Aaron Arnold
Terrace Avenue
Albany, NY 12203

October 6, 1981

"Minneman *et* a/, generously noted recently, 'The pioneering work of Lands and his colleagues represented the first clear evidence that subtypes of β-adrenergic receptors exist'[1] Accordingly, this seems an appropriate time to review the background for our studies.

"Autonomic responses to sympathomimetic amines were segregated into two groups by Ahlquist in 1948[2] with an inspired a- and β-receptor terminology suggestion. The a-receptor ones (vasoconstriction, nictitating membrane contraction, etc.) responded well to epinephrine and to norepinephrine. They responded only minimally, or not at all, to isoproterenol. The β-receptor ones (tracheal and bronchial smooth muscle relaxation, vasodilatation, etc.) responded best to isoproterenol, and well to epinephrine. They responded only weakly to norepinephrine. Ahlquist's suggestion circumvented the inconsistencies that resulted from attempts to classify the responses into excitatory and inhibitory groupings, for example.

"Ahlquist's proposal received important support from Powell and Slater's classical finding[3] that dichloroisoproterenol (DCI) could block the responses of agonists on the β-recepter. This finding complemented a-blocker data and was a reassuring tool in delineating a-receptor from β-receptor responses.

"However, Ahlquist's proposal left a troublesome finding open Mammalian heart responds well to isoproterenol and as well to norepinephrine as to epinephrine.[4] In Ahlquist's scheme norepinephrine was only a minimally effective β-agonist. The discrepancy was minimized by listing the heart's β-receptors as 'exceptions'

"In 1966 data from our group at Sterling-Winthrop Research Institute were presented[5] at the spring Pharmacology Society meetings which showed, with supporting correlation coefficient data, that the responses of the cardiac and lipolytic β-receptors to norepinephrine and certain norepinephrine analogs correlated. Similarly, the responses of the bronchial and vasodepressor β-receptors to the amines correlated. In no instances did the cardiac or lipolytic responses to the above amines correlate with those of the bronchial or vasodepressor ones. In more specific terms, relative to isoproterenol and epinephrine, norepinephrine and nordefrin were effective cardiac and lipolytic stimulants. They were only weak or minimally effective bronchodilators or vasodepressors. Contrariwise, certain vasodepressor amines (N-t-butylnorepinephrine, N-cyclopentylbutanefrine, isoetharine) were effective bronchial and vasodepressor /J-receptor agonists, but were relatively less so on the cardiac and lipolytic β–receptors. The data presented at the spring meetings were published in May 1967 in *Nature* (which is the subject paper of this *Citation Classic)* with the added suggestion that the heart and lipolytic receptor be termed β_1. The bronchial and vasodepressor one was termed β_2. The suggestion appears to have withstood the test of time and, as noted recently,[6] has specifically been termed by a number of investigators to have been 'widely accepted.' Additional instances of sympathomimetic amine responses subserved by the β_1-receptor (coronary and intestinal smooth muscle relaxation, kidney renin release, salivary gland excretion, etc.) and by the β_2-receptor (skeletal muscle contraction and glycogenolysis, pancreatic insulin release, rat diaphragm contraction, etc.) have been summarized.[6]

"The β_1-, β_2-receptor suggestion helps group autonomic responses into anticipated closely related and significantly unrelated effects. The suggestion yields an experimental basis for 'cardiac selective,' or anti-hypertensive selectivity. It provides a rationale for the possible elucidation of additional 'selective' agents while guarding against optimism wherein selectivity may less likely be achieved."

1. **Mimmeman K P, Pittman R N & Molinoff P B.** β-adrenergic receptor subtypes: properties, distribution, and regulation. *Annu. Rev. Neurosci.* **4**:419-61, 1981.
2. **Ahiquist R** P. A study of the adrenotropic receptors. *Amer. J. Physiol.* **153**:586-600, 1948. (Citation Classic. *Current Contents* (45): 16, 6 November 1978.)
3. **Powell C E & Slater I H.** Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol. J. *Pharmacol. Exp. Ther.* **122**:480-8, 1958.
4. **Luduema F P, Ananenko E, Siegmund O H & Miller L C**. Comparative pharmacology of the optical isomers of arterenol. *J Pharmacol. Exp. Ther.* **95**:155-70, 1949.
5. **Arnold A, McAuliff J P, Luduena F P, Brown T G, Jr. & Lands A M.** Lipolysis and sympathomimetic amines. *Fed. Proc.* **25**:500, 1966.
6. **Arnold A.** Sympathoraimetic amine-induced responses of effector organs subserved by a-.β_1- and β_2-adrenoceptors. *Handb. Exp. Pharmacol* **54**:63-88, 1980.