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This Week's Citation Classic®

Berthelsen S & Pettinger W A. A functional basis for classification of α-adrenergic receptors. *Life Sci.* 21:595-606, 1977.
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This was a brief review article consisting of: data from my melanocyte-granule-dispersion experiments in the frog skin conducted in 1964, which were the first pharmacologic demonstration of α_2-adrenergic receptors; and activity ratios for α-adrenergic agonist drugs in various organs and functions, which contributed collectively to the functional identification of two types of α-adrenergic receptors. [The *SCI*® indicates that this paper has been cited in over 730 publications.]

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The experiments that lead to this *Citation Classic* were conducted in Aaron Lerner's laboratory at Yale University in late 1964 and were published in 1977.[1] Results of my studies of methyldopa in humans with Albert Sjoerdsma at the National Institutes of Health in 1962 suggested that metabolites of this drug could substitute for dopamine and/or norepinephrine *in vivo* and led to the "false neurotransmitter" concept of action. However, I did not believe this concept, at least as a peripheral mechanism, since methyldopamine and methylnorepinephrine were nearly equipressor to the naturally occurring catecholamines in man.

As a resident in internal medicine at Yale I had a three-month dermatology rotation with Lerner. He had developed a technique for the study of melanocyte-stimulating-hormone-induced darkening of frog skin, which could be reversed or antagonized by α-adrenergic receptor-agonist drugs. Assuming (erroneously) that all α-adrenergic receptors were alike, I did dose-response curves to a variety of α-adrenergic receptor agonists in this model. Remarkably, the α-methylated metabolites of methyldopa were 30- to 100-fold more potent (rather than less, as presumed by the false neurotransmitter concept) than the naturally occurring catecholamines. These studies, to my knowledge, were the first to pharmacologically demonstrate the α_2-adrenergic receptor and provided the cornerstone for our *Citation Classic*.

The reason for the 13-year delay in publication was that Lerner felt uncomfortable in not understanding these remarkable results. Fortunately, however, evidence accumulated that methyldopa lowered blood pressure by a central nervous system site of action through a receptor similar to that in the frog skin, as suggested in this paper. Still, even though he provided the support, the technician, and the laboratory, Lerner declined coauthorship, claiming that the ideas were uniquely mine.

During 1976 and 1977 this unique α-adrenergic receptor was becoming more interesting to me. I asked Spencer Berthelsen, a medical student working in my laboratory on a summer fellowship, to review the scientific literature for evidence of other α-adrenergic receptors with similar characteristics. This review revealed a widespread similarity among α-adrenergic receptors in other experimental systems. This similarity led to our description of the pharmacologic characteristics of and the classification of α_1- and α_2-adrenergic receptors.

There are several reasons the work was so highly cited. First and foremost, the α_2-adrenergic receptor regulatory role is important in many systems involving cyclic AMP as a mediator of plasma membrane receptor effects. Examples include regulation of lipolysis, insulin release, sodium and water excretion in the kidney and GI tract, and mood and depression and are abnormally regulated in the kidney of genetically hypertensive rats.[2] Second, as simple as our concept was in retrospect, no one had previously put the whole picture together. Once we did this with the melanocyte granule dispersion data, the inhibition of norepinephrine release, and so on, in this *Citation Classic*, the picture was so obvious that nearly everyone accepted it immediately.[3] Finally, timing was obviously important. Prior to our publication everyone thought of α-adrenergic receptors as postsynaptic and prejunctional rather than pharmacologically distinct. Our concept of a broad distribution of α_2-adrenoceptors located on effector organs that mediate apparently suppressive effects (through inhibition of adenylate cyclase) was immediately accepted by most investigators. Within a few weeks of publication, I had many calls and letters from fellow researchers because the concept explained and simplified apparently diverse and conflicting data and perspectives.

I have received the Burroughs Wellcome Scholar Award in Clinical Pharmacology, the Rawls Palmer Progress in Medicine Award, and the Creasy Award in part as a result of the impact of this *Citation Classic*.

1. **Pettinger W A.** Unusual alpha-adrenergic receptor potency of methyldopa metabolites on melanocyte function. *J. Pharmacol. Exp. Ther.* 201:622-6, 1977. (Cited 25 times.)
2. **Pettinger W A, Umemura S, Smyth D D & Jeffries W B.** Renal α_2-adrenoceptors and the adenylate cyclase-cAMP system: biochemical and physiological interactions. *Amer. J. Physiol.* 252:F199-208, 1987.
3. **Timmermans P B M W M & Van Zwieten P A.** α_2-Adrenoceptors: classification, localization, mechanisms, and targets for drugs. *J. Med. Chem.* 25:1389-401, 1982. (Cited 150 times.)