

This Week's Citation Classic®

Kobinger W. Central α -adrenergic systems as targets for hypotensive drugs.
Rev. Physiol. Biochem. Pharmacol. 81:39-100, 1978.
[Ernst-Boehringer-Institut für Arzneimittelforschung, Vienna, Austria]

The review summarized evidence that clonidine represents a novel class of drugs that appear with a typical cardiovascular pattern, triggered by a specific action upon medullary central nervous system sites. The molecular basis of these actions was attributed to a stimulation of medullary α -adrenoceptors. Pharmacological evidence indicated that medullary catecholamines might physiologically modulate cardiovascular depression. [The *SCI*® indicates that this paper has been cited in over 380 publications.]

W. Kobinger
Department of Pharmacology
Ernst-Boehringer-Institute for Drug Research
Dr. Boehringer-Gasse 5-11
A-1121 Vienna
Austria

July 16, 1987

The antihypertensive drug clonidine was originally designed as a nasal decongestant. Its ability to lower blood pressure was serendipitously discovered in Ingelheim, Federal Republic of Germany, when human volunteers got a few drops of the drug into their noses.

In 1961 the late Ernst Boehringer, one of the owners of Boehringer Ingelheim, a drug company, had decided to open a small research institute in Vienna to look for new territories in drug research. In 1965 the pharmacological laboratory in Vienna was asked to investigate the mechanism of action of clonidine. These mechanisms were revealed over the next 10 years by the following steps: localization of the site of action in the central nervous system (CNS) and characterization of the central action pattern as sympathoinhibition plus

vagal activation. These results provided evidence that the central action pattern was due to a stimulation of central α -adrenoceptors; it also provided evidence for the postsynaptic nature of these receptors.

Experiments and discussions grew in a stimulating and exciting atmosphere with my two colleagues, A. Walland (at the beginning) and L. Pichler (in later stages). Similar and complementary work was done in Amsterdam¹ and Paris,² and there was a lively connection between our groups, both competitive and amicable. For pharmacologists these investigations solved the problem of a drug that locally acted as a vasoconstrictor but systemically lowered the blood pressure. It took the medical profession some time to realize that a "sympathomimetic" may serve as an antihypertensive drug.

A review article is a favourite for a *Citation Classic* if the editor selects the suitable author at the right moment. The suitable author is someone who did a lot of original work in the field, causing subsequent authors to cite (or read) all the literature that was published earlier. The right moment is when a new field has reached a certain profile but is still expanding or leading into another exciting direction. When the article mentioned here was written, it became apparent to the researchers in the field that the new, and some old, α -adrenoceptor-stimulating and -blocking drugs did not fit completely into the frame of our textbooks. It followed the discovery of the adrenoceptor subtypes α_1 and α_2 and the relationship to pre- and postsynaptic α -adrenoceptors; clonidine-like drugs played a considerable role in this process. I had the opportunity to review the recent developments on the occasion of the second Rudolf Buchheim Lecture.³ A group of α -adrenoceptor agonists, mentioned previously, were then found to stimulate central dopamine receptors;⁴ this opened up new therapeutic perspectives for the treatment of schizophrenia and morbus Parkinson.⁵

1. van Zwieten P A. Antihypertensive drugs with a central action. *Prog. Pharmacol.* 1:1-63, 1975. (Cited 205 times.)
2. Schmitt H. The pharmacology of clonidine and related products. (Gross F, ed.) *Handbook of experimental pharmacology. Volume 39. Antihypertensive drugs.* Berlin: Springer, 1977. p. 299-396. (Cited 135 times.)
3. Kobinger W. Drugs as tools in research on adrenoceptors. *Arch. Pharm.* 332:113-23, 1986.
4. Andén N-E, Golembiowska-Nikitin K & Thorström U. Selective stimulation of dopamine and noradrenaline autoreceptors by B-HT 920 and B-HT 933, respectively. *Arch. Pharm.* 321:100-4, 1982.
5. Hinzen D, Hornykiewicz O, Kobinger W, Pichler L, Pflü C & Schingnitz G. The dopamine autoreceptor agonist B-HT 920 stimulates denervated postsynaptic brain dopamine receptors in rodent and primate models of Parkinson's disease: a novel approach to treatment. *Eur. J. Pharmacol.* 131:75-86, 1986.

CC/LS

147