

**This Week's Citation Classic**

van Zwieten P. A. Antihypertensive drugs with a central action. (Whole issue.)  
*Prog. Pharmacol.* 1(1), 1975. 63 p.  
[Laboratorium voor Farmacie, Universiteit van Amsterdam, Afdeling Farmacotherapie,  
The Netherlands]

This review paper deals with drugs that lower blood pressure owing to their effect on the brain centres, neurones, and adrenoceptors, which are involved in the central nervous system regulation of blood pressure and heart rate. Clonidine, guanfacine, and  $\alpha$ -methyl-DOPA (which is converted in the brain into  $\alpha$ -methylnoradrenaline) are the prototypes of the centrally acting antihypertensives. They stimulate central  $\alpha_2$ -adrenoceptors and hence reduce peripheral sympathetic tone and blood pressure. [The *SCI*<sup>®</sup> indicates that this work has been cited in over 245 publications, making it the most-cited paper published in this journal.]

P.A. van Zwieten  
Division of Pharmacotherapy  
Academic Medical Centre  
University of Amsterdam  
1105 AZ Amsterdam  
The Netherlands

February 23, 1988

The recognition that the brain plays an important role in cardiovascular control prompted the search for drugs that lower blood pressure via a primary target in the central nervous system. This search was greatly facilitated by the development of refined methods, allowing the injection of small amounts of the drugs to be tested into the appropriate brain regions. Circulatory effects of the drugs after application to the brain can subsequently be compared quantitatively with effects obtained after injection of the drugs into the systemic circulation. A suitable method for this purpose, which we developed, is the injection of drugs into the left thoracic vertebral artery (VA) of the cat. This method, although technically and surgically more difficult, is preferable to intracarotid administration of drugs, since the VA predominantly perfuses the ponto-medullary region of the brain, where the relevant centers involved in central nervous cardiovascular control are located.

The basic experimental findings that greatly stimulated us to perform research on centrally acting antihypertensives and their mode of action were the following: extremely low doses of clonidine, guanfacine, or  $\alpha$ -methyl-DOPA,

when injected into the VA, caused a pronounced and prolonged fall in arterial blood pressure, whereas the same or even much higher doses proved ineffective when applied to the systemic circulation. The mode of action of the drugs could be analysed by means of appropriate agonists and antagonists and may be summarized as follows: clonidine, guanfacine, and  $\alpha$ -methylnoradrenaline (from  $\alpha$ -methyl-DOPA) are agonists towards  $\alpha_2$ -adrenoceptors in the brain stem. The stimulation of the  $\alpha_2$ -adrenoceptors involved causes a depression of peripheral sympathetic tone, probably via the activation of a bulbo-spinal neuron. The depressed peripheral sympathetic tone, as reflected by low plasma catecholamines, readily explains the fall in blood pressure and heart rate caused by the aforementioned drugs. Sedation and dry mouth, the most common side effects of the centrally acting drugs, are also mediated via  $\alpha_2$ -adrenoceptors, though in other anatomical regions than those involved in central cardiovascular control.

The concept of central  $\alpha_2$ -adrenoceptors as the primary target of clonidine and related drugs also explains the well-known interaction between these drugs and tricyclic antidepressants. The central hypotensive action of clonidine and similarly acting agents, mediated by  $\alpha_2$ -adrenoceptor stimulation, is diminished or abolished by various tricyclic antidepressants (imipramine and related compounds) because they are  $\alpha_2$ -adrenoceptor antagonists, also at the level of the central  $\alpha_2$ -adrenoceptors.

The concept of central  $\alpha_2$ -adrenoceptors as the basis of central hypotensive activity was developed simultaneously, and in friendly competition, by the research teams of W. Kobinger<sup>1</sup> (Vienna), H. Schmitt<sup>2</sup> (Paris), and by us (Amsterdam). Since the publication of the 1975 review paper many new findings have been recorded that, however, have not fundamentally changed the classical concept. Among the newer findings we would like to mention: (1) the identification of the central  $\alpha_2$ -adrenoceptors as belonging to the  $\alpha_2$ -subtype, probably located at postsynaptic sites;<sup>3</sup> and (2) a quantitative analysis of the structure-activity relationship concerning the agonists that interact with the central  $\alpha_2$ -adrenoceptor, thus allowing a detailed description of the receptor.<sup>4</sup>

1. Kobinger W. Central  $\alpha_2$ -adrenergic systems as targets for hypotensive drugs. *Rev. Physiol. Biochem. Pharmacol.* 81:39-100, 1978. (Cited 385 times.) [See also: Kobinger W. Citation Classic. *Current Contents/Life Sciences* 30(50):17, 14 December 1987.]
2. Schmitt H. Action des  $\alpha$ -sympathomimétiques sur les structures nerveuses (Effects of  $\alpha$ -sympathomimetics on nerve structures). *Actual. Pharmacol.* 24:93-131, 1971. (Cited 65 times.)
3. van Zwieten P A & Timmermans P B M W M. Central and peripheral  $\alpha_2$ -adrenoceptors, pharmacological aspects and clinical potential. *Advan. Drug Res.* 13:209-54, 1984. (Cited 15 times.)
4. Timmermans P B M W M, Hoefke W, Stähle H & van Zwieten P A. Structure-activity relationships in clonidine-like imidazolidines and related compounds. (Whole issue.) *Prog. Pharmacol.* 3(1), 1980. 97 p. (Cited 50 times.)