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 α-methylnoradrenaline (which is converted into the brain into α-methylnoradrenaline) are the prototypes of the centrally acting antihypertensives. They stimulate central α₂-adrenoceptors and hence reduce peripheral sympathetic tone and blood pressure. [The SCI* indicates that this work has been cited in over 245 publications, making it the most-cited paper published in this journal.]

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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 α-methylnoradrenaline, 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 α-methylnoradrenaline (from α-methylnoradrenaline) are agonists towards α₂-adrenoceptors in the brain stem. The stimulation of the α₂-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 α₂-adrenoceptors, though in other anatomical regions than those involved in central cardiovascular control.

The concept of central α₂-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 α₂-adrenoceptor stimulation, is diminished or abolished by various tricyclic antidepressants (imipramine and related compounds) because they are α₂-adrenoceptor antagonists, also at the level of the central α₂-adrenoceptors.

The concept of central α₂-adrenoceptors as the basis of central hypotensive activity was developed simultaneously, and in friendly competition, by the research teams of W. Kobinger1 (Vienna), H. Schmidt² (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 new findings we would like to mention: (1) the identification of the central α₂-adrenoceptors as belonging to the α₂-subtype, probably located at postsynaptic sites; and (2) a quantitative analysis of the structure-activity relationship concerning the agonists that interact with the central α₂-adrenoceptor, thus allowing a detailed description of the receptor.*