CLONIDINE, an \( \alpha_2 \)-adrenergic receptor agonist, lowers arterial pressure (AP) by centrally inhibiting sympathetic nerve activity. The sympathoinhibitory action of clonidine, and related drugs rilmenidine and moxonidine, are believed to result from inhibition of tonically active sympatoexcitatory reticulospinal neurons of the rostroventrolateral medulla (RVLM) (24). Central inhibition of sympathetic activity has advantages in the treatment of hypertension by decreasing release of renin as well as peripheral resistance (5). In peripheral tissues, clonidine is an agonist at \( \alpha_2 \)-adrenergic receptors (\( \alpha_2 \)AR) (26). It was therefore originally assumed that clonidine's hypotensive actions were attributable to stimulation of central \( \alpha_2 \)AR. However, even as early as 1976, Karppanen et al. (15) hypothesized that the antihypertensive actions of clonidine administered intracerebroventricularly related to nonadrenergic receptors, possibly histaminergic. More recently, the central effects of clonidine have been attributed to novel imidazoline receptors (6, 28, 32), some of which might be related to amine oxidases (21) or nicotinic ion channels (20).

In an important structure-function analysis in 1984, Bousquet et al. (2) directly tested the non-\( \alpha_2 \)AR hypothesis of clonidine's action. They compared the activity of a panel of drugs to lower AP when microinjected into the RVLM of anesthetized cats. The drugs differed in their actions at known catecholaminergic receptors and in their chemical structures. It was noted that the hypotensive potencies of these drugs related to whether or not they contained an imidazoline ring structure, not necessarily to their affinities at \( \alpha_2 \)AR. It was therefore proposed that clonidine lowered AP by an interaction in the ventral medulla with "sites preferring the imidazoline structure" (I sites).

The original concept for imidazoline receptors proposed by Bousquet et al. (2) has been supported by two principal lines of investigation. First, the antihypertensive actions of agents injected into the RVLM of conscious animals have been correlated with radioligand binding affinities to I1 sites, but not \( \alpha_2 \)AR, as measured in membranes of ventral medulla (6). Although Bousquet's initial study was criticized because of the possible metabolism of microinjected norepinephrine (29) and because of other possible pathways of action (27), recent studies (3, 12) have upheld the proper rank ordering of affinities to subtype I1-binding sites versus hypotensive efficacies, without including catecholamines or imidazole acetic acid in the correlation. Second, the central administration of imidazolines, either intracerebroventricularly (4, 13) or by microinjection into RVLM (9, 22), blocks the antihypertensive actions of systemically administered clonidine and/or rilmenidine or moxonidine. In contrast, a number of selective \( \alpha_2 \)-antagonists appear to have either weak or no blocking effects. Finally, the concept that hypotension relates to stimulation of an imidazoline receptor has found therapeutic use. The development of rilmenidine and moxonidine, by favoring binding to I sites rather than \( \alpha_2 \)AR, has minimized the most limiting side effect of clonidine, namely somnolence, attributable to \( \alpha_2 \)AR (30).
The evidence appears strong that imidazoline-binding sites and $\alpha_2$-AR are physically distinct entities. Candidate proteins for imidazoline receptors have been isolated (32) that are not related to $\alpha_2$-AR. Second, $\alpha_2$-AR- and imidazoline-binding sites (I1 and I2) can be differentially downregulated by chronic drug treatments in vivo (11). I1- and $\alpha_2$-AR-binding sites also differ in regard to their responses to GTP (8). Recently, I1 receptor activation was linked to diacylglycerol accumulation via phosphorylcholine-phospholipase C activation, making ultimate expression via arachidonic acid release (28). This pathway has not been previously ascribed to an $\alpha_2$-adrenoceptor.

On the other hand, other studies have suggested that the effects on AP of clonidine-like drugs may be entirely attributable to stimulation of $\alpha_2$-AR. The first line of evidence is that when selective $\alpha_2$-antagonists are administered systemically, rather than centrally, the antihypertensive responses to intravenous clonidine are totally blocked (14, 31). Second, the discharges of neurons (single cells) in RVLM, expressing $\alpha_2$-AR (25), are inhibited by systemic and/or iontophoretic application of either catecholamines or clonidine (1, 25). Moreover, these effects are antagonized by iontophoretic application of methoxy-idozoxan, a drug that most investigators, except Ernsberger and Haxhiu (7), believe is a selective $\alpha_2$-antagonist. Third, transgenic mice expressing mutated $\alpha_2$-AR, with intact $\alpha_2$-AR and $\alpha_2C$-AR subtypes of $\alpha_2$-AR, were reported (17, 18) to lack hypertensive responses to two imidazolines, one of which was clonidine (Dr. Lee Limbird, Vanderbilt University; personal communication).

It is also noteworthy to realize that ligands for I sites are not limited to imidazolines, but include guanidiniums (e.g., guanabenz, agmatine), an oxazole (e.g., rilmenidine), and a bicycloheptane, AGN-192403 (19). Most I site ligands potently agonize or antagonize hypotensive responses when administered centrally, except agmatine (a putative endogenous ligand for I sites) and the bicycloheptane (19, 23). The latter two drugs possess moderate (agmatine) to high (AGN-192403) affinities at I sites but lack hypertensive potentials in vivo (16, 19). However, selective $\alpha_2$-agonists (e.g., guanaben) and $\alpha_2$-antagonists (e.g., SKF-86466) exist that are nearly devoid of affinity at I1-binding sites.

In two accompanying articles (7, 10), these divergent viewpoints are presented. Dr. Patrice Guyenet presents the traditional viewpoint that clonidine’s hypotensive action can be explained sufficiently by postsynaptic $\alpha_2$-AR. On the other side of the debate, Drs. Paul Ernsberger and Musa A. Haxhiu contend that clonidine and other imidazolines act primarily via imidazoline receptors in the RVLM.

Address for reprint requests: D. J. Reis, Cornell University Medical College, 411 East 69th St., Rm. KB 410, New York, New York 10021.

REFERENCES


