The imidazoline receptor in control of blood pressure by clonidine and allied drugs

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Reis, Donald J., and John E. Piletz. The imidazoline receptor in control of blood pressure by clonidine and allied drugs. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1569–R1571, 1997.—Clonidine, moxonidine, and rilmenidine are centrally acting antihypertensive agents that lower arterial pressure by inhibiting the tonic activity of sympathoexcitatory neurons in the rostral ventrolateral medulla. Competing hypotheses have been put forward by different investigators to explain the sympathoinhibition evoked by “imidazoline drugs”: either via central actions at \(\alpha_2\)-adrenergic receptors or novel I\(_1\)-imidazoline receptors. These different perspectives are presented in the accompanying reviews.

ventrolateral medulla; arterial pressure; \(\alpha_2\)-adrenergic receptors

**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 sympathoexcitatory reticulospinal neurons of the rostroventrolateral medulla reticular nucleus of the medulla oblongata (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 agents injected into the RVLM of conscious animals have been correlated with radioligand binding affinities to I 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 I\(_1\)-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 α2-AR are physically distinct entities. Candidate proteins for imidazoline receptors have been isolated (32) that are not related to α2-AR. Second, α2-AR- and imidazoline-binding sites (I1 and I2) can be differentially downregulated by chronic drug treatments in vivo (11). I1- and α2-AR-binding sites also differ in regard to their responses to GTP (8). Recently, I1 receptor activation was linked to diacylglycerol accumulation via phosphatidylinositol-phospholipase C activation, making ultimate expression via arachidonic acid release (28). This pathway has not been previously ascribed to an α2-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 α2-AR. The first line of evidence is that when selective α2-antagonists are administered systemically, rather than centrally, the antihypertensive responses to intraventricular clonidine are totally blocked (14, 31). Second, the discharges of neurons (single cells) in RVLM, expressing α2-AR (25), are inhibited by systemic and/or iontophoretic application of either catecholamines or clonidine (1, 29). Moreover, these effects are antagonized by iontophoretic application of methoxy-idazoxan, a drug that most investigators, except Ernsberger and Haxhiu (7), believe is a selective α2-antagonist. Third, transgenic mice expressing mutated α2-AR, with intact α2A-AR and α2C-AR subtypes of α2-AR, were reported (17, 18) to lack hypotensive 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 clonidine and rilmenidine. In I sites and the bicycloheptane (19, 23), the latter two drugs possess moderate (agmatine) to high (AGN-192403) affinities at I sites but lack hypotensive potencies in vivo (16, 19). However, selective α2-agonists (e.g., guanabenz) and α2-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 α2-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.

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REFERENCES


