SUMMARY It has been well established that the antihypertensive drugs clonidine and methyldopa lower blood pressure by acting on postsynaptic \( \alpha_2 \)-adrenergic receptors within cardiovascular control centers of the brain. A number of novel agents designed as lipophilic and highly selective \( \alpha_2 \)-adrenergic stimulants have been synthesized and in general the pharmacological features of these agents resemble clonidine or \( \alpha \)-methylnorepinephrine, the principal metabolite of methyldopa. The clonidine analogs, ICI-106,270, UK-14,304, piclonidine (LR-99,853), and the bridge analogs (ST-1913, ST-1966, ST-1967) exhibit varying activity on the central cardiovascular control centers. ICI-106,270 is of interest because relative to clonidine it appears to exert fewer CNS side effects. Azepexole (BHT-933) is also of interest because, although structurally unrelated to clonidine, it appears to interact with central \( \alpha \)-adrenergic receptors in a manner similar to that of clonidine. In contrast, central administration of ST-1966, a monoatomic bridge analog of clonidine, lowers blood pressure in animals treated with an \( \alpha_2 \)-antagonist, which suggests other mechanisms may be involved in its action. Novel antihypertensive agents structurally similar to methyldopa have not been described, although viable prodrugs of methyldopa such as 2-oxo-1,3-dioxol-4-yl-methyl and pivaloyloxyethyl esters have been shown to have greater oral activity than methyldopa, presumably because they are more lipophilic than the parent moiety. \( \alpha \)-Monofluoromethyldopa, a highly potent and irreversible inhibitor of aromatic amino acid decarboxylase, has interesting central properties related to catecholamine depletions and inhibition of dopa-decarboxylase, but because this agent is not metabolized to the corresponding fluorinated catecholamine, a central antihypertensive response similar to methyldopa could not be demonstrated in spontaneously hypertensive rats. Tyrosine prodrugs may offer another approach to reducing blood pressure centrally, although their precise mechanism is not understood. In summary, newer and more selective \( \alpha_2 \)-adrenergic receptor agonists have been described, but none of these agents appears to be totally free from the sedative liability of clonidine and methyldopa.

**KEY WORDS** • clonidine • methyldopa • CNS • \( \alpha_2 \)-agonists • antihypertensive drugs

In recent years a large effort has been expended in improving the efficacy, receptor selectivity, and side effect profile of methyldopa and clonidine. Advances in radioligand-binding technology have aided medicinal chemists in designing novel molecules with greater selectivity and affinity, and the introduction of selective \( \alpha_2 \)-adrenergic antagonists has been instrumental in helping the pharmacologist define the specific adrenergic receptor subtype involved in the centrally mediated blood pressure and sedative effects of new clonidine derivatives. This report describes some of the recent progress in developing new lipophilic \( \alpha \)-adrenergic agonists, which are claimed to have a greater separation than clonidine between the doses that reduce blood pressure and those that cause sedation. Efforts to develop prodrugs of methyldopa and tyrosine will be described as well as some recent experimental work with the irreversible dopa-decarboxylase inhibitor \( \alpha \)-monofluoromethyldopa.

**Bridge Analogs of Clonidine**

In this series of imidazolines, the bridging nitrogen atom of clonidine has been replaced with a sulfur (ST-1967) or an oxygen (ST-1966) atom. ST-1913, the methylene bridge analog of clonidine, has been the most extensively studied compound of this series.\(^1\)\(^3\) This modification produced a large alteration in the physicochemical properties of the molecule, but this compound had about the same activity as clonidine on \( \alpha_2 \)- or \( \alpha_1 \)-adrenergic receptors, based on in vitro experiments in the guinea pig ileum or aorta\(^2\) or on its ability to displace specific \(^3\)H]-clonidine binding sites from rat brain membranes.\(^4\) Interestingly, Timmer-
mans et al. demonstrated that ST-1913 administered by vertebral artery infusion was less active than clonidine in cats and that, unlike ST-1966 and ST-1967, the centrally induced hypotension with ST-1913 was antagonized by the \( \alpha_2 \)-blocker piperoxan. Ruffolo et al. observed that clonidine was about 25-fold more potent than ST-1913 after intravenous injection in spontaneously hypertensive rats (SHR), but both compounds were similar in their ability to lower blood pressure when administered beyond the blood-brain barrier (intracisternal administration). Because of pKa considerations (clonidine = 7.7; ST-1913 = 9.7), a greater percentage of clonidine exists in the un-ionized form relative to ST-1913; therefore, it is more likely to penetrate the blood-brain barrier. Definitive sedation studies have not been reported for members of this series.

**Clonidine Analogs with Chemical Modification on Bridge Nitrogen**

Piclonidine (LR-99,853), \((-)-2-[2,6-dichloro-N-(tetrahydro-2H-pyran-2-yl) anilino]-2-imidazoline\), has been demonstrated to be as potent as clonidine in lowering blood pressure in rats by the oral route. Unlike clonidine, however, its hypotensive action was not preceded by a pressor phase, and the hypertensive phase occurred more gradually and was generally longer lasting than in clonidine. By the intravenous and intracerebroventricular (i.c.v.) routes, piclonidine was significantly less active than clonidine and caused no sedation at 1 mg/kg p.o. Because full dose-response curves were not reported, the separation between the hypotensive and sedative effects of the compound could not be accurately ascertained. The dose of piclonidine that reduced blood pressure by 10% (0.2 mg/kg p.o.) was considerably lower than that required to inhibit GI motility and induce mydriasis and hyperglycemia. These findings suggest that piclonidine may be somewhat more selective than clonidine.

Hepatic metabolism was involved in generating an active moiety that apparently is not clonidine nor a clonidine metabolite. Consistent with a produg profile of action are studies that demonstrated a delay in the onset of action, the lack of the early phase of hypotension, and lower CNS depressive activity.

Another agent that has a chemical substitution on the bridge nitrogen is the N-allyl derivative of clonidine ST-567, or alinidine \([2-N-allyl-N-(2,6-dichlorophenyl)amino]-2-imidazoline\). In anesthetized cats and dogs the most prominent action of this agent was a pronounced bradycardic action. Alinidine, 80 mg p.o., produced tiredness and dry mouth in humans. Although these side effects are similar to those found with clonidine, a produg explanation has been ruled out as the compound is excreted unchanged in humans.

**Other Clonidine Analogs**

IFIC-106, 270, \(6-[2-chloro-6-fluorophenyl]-2,3,6,7-tetrahydro-5H-pyrrolo-[1,2-a]-imidazole\) hydrobromide) was designed as a lipophilic \( \alpha \)-adrenergic stimulant, and early studies indicated that unlike clonidine this agent had some separation between antihypertensive and sedative properties in anesthetized rats clonidine reduced blood pressure by 20 mm Hg at 1.2 \( \mu \)g/kg i.v., whereas a similar reduction in blood pressure was evident at 5.5 \( \mu \)g/kg i.v. with ICI-106,270. Clonidine produced sedation in rats at 15.3 \( \mu \)g/kg i.v., whereas for ICI-106,270, a similar level of sedation was observed at 238 \( \mu \)g/kg i.v. Thus, the ICI \( \alpha \)-adrenergic agonist was about 15 times less potent than clonidine as a sedative but only 4.5 times less potent as a hypotensive.

Another important difference from clonidine was that the ICI compound displayed little overshoot of blood pressure on sudden withdrawal. The basis of the differences in activity of the ICI compounds, and particularly on sedation parameters versus blood pressure, is not entirely clear. Differences between the ICI series and clonidine in terms of penetration into the CNS seem unlikely, as they have similar lipid solubilities and thus should readily pass the blood-brain barrier. Most researchers who have evaluated clonidine agree that both sedation and hypotension are mediated via \( \alpha \)-adrenergic receptors, but there is less agreement about ascribing these effects to either \( \alpha_1 \) or \( \alpha_2 \)-adrenergic receptors. After studying the ICI compounds, Clough and Hatton maintained that the hypotensive activity of this series appears to be more closely related to \( \alpha_1 \)-than to \( \alpha_2 \)-potency of these compounds. These workers, however, could not precisely classify the type of \( \alpha \)-adrenergic receptor involved in mediating the sedative effects of these compounds.

UK-14,304 (5-bromo-6-[2-imidazoline-2-ylamino]-[5,4-d]-azepin-dihydrochloride) or BHT-933 was designed as a lipophilic \( \alpha \)-adrenergic agonist. Unlike clonidine, it is a full agonist and its \( \alpha \)-adrenergic agonist properties have been demonstrated in the guinea pig ileum and rabbit pulmonary artery. The high selectivity of UK-14,304 for \( \alpha_1 \)-adrenergic receptors has been confirmed in pithed rats and in ligand binding studies. In rat brain membranes, 1 nmol UK-14,304 displaced bound \( [\text{H}] \)-clonidine (\( \alpha_2 \)-adrenergic agonist) by 50%, whereas as a concentration of 1 \( \mu \)mol was needed to displace bound \( [\text{H}] \)-prazosin (\( \alpha_1 \)-adrenergic agonist) by an equivalent amount. In a double-blind clinical study comparing oral clonidine (0.3 mg) and UK-14,304 (0.75 mg), Ashton and Rawlins found that both clonidine and UK-14,304 caused a progressive increase in the subjective ratings of sleepiness, which was maximal 2 to 4 hours after treatment. According to these researchers, UK-14,304 was less depressant than clonidine, but it also had a less marked hypotensive effect.

Most of the compounds previously described in this review show structural similarities to clonidine. Azepexole (2-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazolo-[5,4-d]-azepin-dihydrochloride) or BHT-933 was developed from a chemical group of substances with antihypertensive properties that coincidentally lowered blood pressure in rats. In cats and rats azepexole caused pronounced hypotensive effects accompanied by bra-
An involvement of central α-adrenergic receptors in its action seems justified from studies with piperoxan. In normotensive people, 10 mg of azepxole and 0.15 mg of clonidine produced similar hypotensive effects. A dose-dependent sedation and dryness of mouth were observed with both agents. Thus, azepxole, although a structurally unique compound, was not free of troublesome CNS side effects.

**Ester Progenitors of Antihypertensive Amino Acids**

Methyldopa is variably and incompletely absorbed in humans. One strategy that has been successful in enhancing the absorption of biologically active chemical species has been to increase lipid solubility by incorporating different esters into molecules. Lipophilic progenitors of methyldopa, the α-pivaloyloxyethyl (POE) and the 1,3-dioxolanylmethyl ester, have been described. It was predicted that the prodrug form (compared with the polar amino acid) would be better absorbed than methyldopa because of better gut transport. In SHR single doses of the pivaloyloxyethyl (POE) ester of methyldopa were somewhat more active than the parent compound in lowering blood pressure. As shown on Figure 1, the onset of action of this agent occurs somewhat sooner than for methyldopa, but the duration of action does not appear to be different for these agents. Previous work from our laboratories has indicated that this ester is approximately 2 times more potent than methyldopa in lowering blood pressure in unanesthetized SHR. The 1,3-dioxolonanylmethyl ester has been synthesized recently; it was also highly active in reducing blood pressure in SHR (Figure 2) but compared with the POE ester its onset of action was comparable to the parent drug.

Administered to healthy volunteers, the POE ester of methyldopa was hydrolyzed on the first pass. The delivery of methyldopa POE in plasma in one study was more uniform compared with that of orally admin-
Acute antihypertensive effect of methyldopa (Aldomet) and the 1,3 dioxolonylmethyl ester of methyldopa in unanesthetized SHR. A 58 mg/kg p.o. dose of this ester is equivalent to 25 mg/kg p.o. of methyldopa. All mean arterial pressure values in the three groups were significantly different from the control value at time 0, p < 0.05. Top panel: ○ Methyldopa, 50 mg/kg p.o.; ● Vehicle (HMC); Bottom panel: ● 58 mg/kg p.o.; ○ 116 mg/kg p.o.; □ 232 mg/kg p.o.

Tyrosine is another amino acid that has received attention because of its possible central antihypertensive properties. We have evaluated the acute antihypertensive effects of L-tyrosine given intraperitoneally and orally to SHR. Although tyrosine was active by the intraperitoneal route (100 and 200 mg/kg) it was inactive orally up to 400 mg/kg. One prodrug, the 2,2-dimethyl-1-oxopropoxyethyl ester, lowered mean arterial pressure (MAP) in SHR both acutely on Day 1 (22 ± 5 mm Hg decrement) and consistently over 3 days (21 to 25 mm Hg decrement). The rate of hydrolysis and thus the stability of the ester linkage was assessed for four different esters to determine if there was a correlation between oral activity and the rate of generation of tyrosine. Two of these esters had approximately the same hydrolysis rate yet differed substantially in oral activity, which suggests that other factors may be influencing absorption, distribution, or penetration in the CNS. There have been no systematic studies to determine whether tyrosine produces undesirable CNS side effects. From our experience, SHR treated with tyrosine esters did not appear sedated as they often do after equivalent antihypertensive doses of methyldopa.

α-Monofluoromethyldopa

The decarboxylation of L-dopa to dopamine by dopa-decarboxylase is a critical step in the biosynthesis of norepinephrine, but because intraneuronal activity of this enzyme is in excess of that for tyrosine hydroxylase, inhibition of this step by inhibitors such as carbidopa or benserazide does not result in either a reduction of neurotransmitter stores or significant lowering of blood pressure. DL-α-Monofluoromethyldopa and S-α-fluoromethyldopa have been synthesized recently and these compounds, through the principle of enzyme-activated irreversible inhibition, produced complete inhibition of the enzyme and substantially depleted tissue catecholamines. Fozard et al. and Johansson and Henning have described some of the biological characteristics of this agent.
These include penetration into the CNS, depression of peripheral sympathetic nervous function, depletion of peripheral stores of norepinephrine, sedation, and blood pressure interactions with L-dopa. Unlike methyldopa the α-fluorinated amino acid is not metabolized to the corresponding fluorinated catecholamines. Figure 3 shows data in unanesthetized SHR from our laboratories that are consistent with this conclusion. Methyldopa produced a dose-related fall in blood pressure after intracerebroventricular injections in SHR. In contrast, α-fluoromethyldopa did not act as a depressor over 24 hours in SHR and, in fact, actually elevated blood pressure; this elevation persisted for approximately 6 hours. The advantage of α-fluoromethyldopa seems to be that it causes selective inhibition of dopa-decarboxylase, but as expected both endogenous catecholamine and serotonin stores were reduced. Its antihypertensive mechanism of action is best explained by a depletion of peripheral and central catecholamine stores, which results in a diminution of sympathetic function (Ulm, E.H. and Smith, P. et al., unpublished observations).

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