SUMMARY

This symposium reviewed the fundamental principles, pharmacology, and clinical pharmacology of central α-adrenergic blood pressure regulating mechanisms. The symposium discussed the role of arterial baro- and chemoreceptor signals in regulating blood pressure. These signals reach the nucleus of the tractus solitarius (NTS) via vagal and glossopharyngeal afferents. The NTS communicates with sympathetic preganglionic neurons in the spinal cord via centers and tracts in the medulla, pons, and hypothalamus that include an α-adrenergic inhibitory network. Descending tracts emphasized in this symposium originate in the C-1 epinephrine cells of the medulla, B-1 and B-3 serotonin cells of the medulla, and A-5 norepinephrine cells of the pons. Transmitters involved are norepinephrine, epinephrine, serotonin, glutamate, and gamma-aminobutyric acid (GABA). Catecholamine enzymes share protein domains in their primary structures and may be coded for by linked or single genes. New methods of purifying and locating α- and β-receptors have been developed.

Pharmacology

Methyldopa, clonidine, and clonidine-like drugs lower blood pressure by stimulating postsynaptic α2-receptors in a brain stem inhibitory network, which down-regulates these receptors. α1-receptors were found to be higher in normotensive than in hypertensive rats and were increased in the latter by methyldopa administration. α2-receptors were found to differ in various tissues, which permits the development of highly selective agonists and antagonists. Although α-methylnorepinephrine is probably the principal metabolite of methyldopa, α-methylepinephrine and α-methyldopamine may also contribute. The site of action usually is identified as the NTS. Possible roles for the descending tracts were suggested.

Clinical pharmacology

Methyldopa, clonidine, guanfacine, and related drugs lower blood pressure principally by CNS mechanisms but peripheral actions may also contribute. Growth hormone concentrations do not increase in hypertensive patients with central α-agonist administration. In animal and clinical studies, the withdrawal reaction was prominent with clonidine, modest with guanfacine, and negligible with methyldopa. Related were decreases in central α2-receptors and rapid eye movement, or REM, sleep. Blood pressure lowering is brought about by balanced reductions in peripheral vascular resistance and cardiac output with preservation of blood flow to vital organs. Reversal of left ventricular hypertrophy in animals without loss of contractility was demonstrated at antihypertensive doses with methyldopa. The beneficial influence of methyldopa and other agents on the natural history of hypertension was described in a report on 15 years of experience.

Key Words

blood pressure • central neurotransmitters • adrenergic • α2-receptors • serotoninergic • methyldopa • clonidine

This symposium stems from an extramural research program generated and sponsored by the Merck Sharp & Dohme Research Laboratories to acquire more information about the central mechanism of action of methyldopa. Although acknowledged for the past 15 years to exert its antihypertensive effects via the brain, information relative to the exact site(s) and metabolites involved has not been precise. The central mechanism of clonidine, although synthesized more recently, has been investigated more thoroughly because of its direct and immediate effects. Indeed, recognition of the sympathoinhibitory actions of clonidine and related drugs primarily are responsible for identifying the role of brain α-adrenergic mechanisms in blood pressure regulation and for confirming earlier concepts of methyldopa action.

These pharmacological studies, plus information from electrophysiological, histochemical, retrograde transport, and nerve degeneration investigations, provide...
the basis of the current understanding of the brain in blood pressure regulation. Much of this information was supplied by research centers represented by persons in this program.

This symposium addresses central blood pressure-regulating mechanisms with special reference to the role of the adrenergic nervous system, α-adrenergic receptors, and antihypertensive agents that affect these entities. The purpose of this presentation is to summarize the information presented by previous speakers in the context of current concepts.

**Fundamental Principles**

Several recent reviews and papers have described the functional anatomy of central pathways concerned with cardiovascular regulation (Figure 1). Readers are directed to these publications for original references. Localization of catecholaminergic and serotonergic nerve terminals is based on the classic histofluorescence studies of Dahlstrom and Fuxe. It is generally agreed that arterial baro- and chemoreceptors, cardiopulmonary low pressure receptors, and lung inflation receptors sense the state of the cardiovascular and respiratory systems and provide this information to the nucleus of the tractus solitarius (NTS) in the medulla via glossopharyngeal and vagal afferents. The NTS also receives input from the cerebellum, hypothalamus, stria terminalis, area postrema, and cerebral cortex and is thus in a position to integrate all these influences and signal other CNS centers to effect circulatory homeostasis. It also is generally agreed that the cell bodies of sympathetic preganglionic neurons (SPNs) are in or near the intermediolateral (IML) cell columns of the thoracolumbar spinal cord. Axons leave the cord in the ventral roots to join the sympathetic ganglia. The corresponding vagal cell bodies are in the nucleus ambiguus and possibly in the dorsal motor nucleus of the vagus. What is not clear are the pathways and transmitters employed by impulses that arise in the NTS to stimulate or inhibit SPNs in the IML cell columns. The organization within the NTS is complex and viscerotopically structured. The papers cited previously described projections from the NTS to the nucleus ambiguus, dorsal motor nucleus of the vagus, hypothalamus, medial accessory olive, and ventrolateral pressor area of the medulla and the spinal cord, which include the IML cell columns. Many of the centers receiving NTS projections have also been shown to be the source of nerve tracts that descend to the IML cells. Principal among these are the C-1 cells in the ventrolateral reticular formation and the ventral raphe nuclei of the medulla, the A-5 cells and parabrachial nuclei of the pons, and the paraventricular nuclei and lateral and posterior areas of the hypothalamus. It is to be emphasized that all levels of the CNS participate in cardiovascular regulation in a highly integrated fashion. For a pathway to be identified with baroreceptor responses, however, one would expect it to include catecholaminergic tracts and an α-adrenergic inhibitory component. This notion is based on experimental studies with 6-hydroxydopamine (6-OHDA),
which destroys catecholaminergic neurons, and experimental and clinical studies with α-adrenergic agonists. The former demonstrated a facilitary role for noradrenergic neurons in baroreceptor responses and the latter, inhibition by α-receptor stimulation. Furthermore, as noted in the paper by Korner et al., the circulatory effects of intravenously and intracisternally (i.c.) administered methyldopa in rabbits resembled those of the acute transmitter release phase of i.e. 6-OHDA administration and were abolished after 2 weeks, when widespread destruction of central noradrenergic neurons had occurred. The concept of a central baroreceptor reflex system that includes inhibitory interneurons has been expressed by Chalmers. 

Reis and colleagues propose that baroreceptor afferent fibers engage NTS cells with L-glutamate as the transmitter, the NTS cells then link via GABAergic transmission to the C-1 epinephrine cells in the ventrolateral medulla, which in turn descend to synapse with cholinergic SPNs in the spinal cord. In sympathetic ganglia, the SPNs activate postganglionic neurons that, of course, release norepinephrine. This hypothesis is consistent with several recent observations.

Although the NTS projects to the spinal cord and contains noradrenergic neurons, which correspond to the A-2 group of Dahlstrom and Fuxe, the spinal cord projections are not noradrenergic according to Blessing and co-workers. These researchers identified the catecholamine (probably noradrenergic) neurons, which reach the cord, as arising almost exclusively from the pons; however, the catecholaminergic neurons in the ventrolateral medulla have been shown to contain phenylethanolamine N-methyltransferase (PNMT), and thus probably synthesize epinephrine. Because epinephrine is not detected by the commonly employed fluorescence techniques, these tracts could have escaped anatomical identification until now. The importance of the ventrolateral medulla in vasomotor
control also has been recognized by Dampney and Moon. These investigators showed that stimulation of this area directly or by ischemia evokes a pressor response and ablation leads to a profound fall in blood pressure.8, 10

Among the major noradrenergic neurons that reach the IML cell columns are those arising in the A-5 cell group of the pons.8, 10 Korner and associates have presented evidence that this tract is part of the pathway mediating methyldopa bradycardia. This evidence is not inconsistent with the views of Reis and co-workers, as all catecholaminergic neurons could be affected by methyldopa metabolites and other a-adrenergic agonists.

Korner et al., also reported that destruction of brain stem noradrenergic neurons abolish, while destruction of serotonergic (5-HT) neurons attenuate, the falls in blood pressure and heart rate produced by i.c. methyldopa. Korner and Head previously reported that noradrenergic and serotonergic neurons each affect both vagal and sympathetically mediated baroreflex actions.17 The bulbospinal pathways controlling blood pressure are seen by these investigators as one set of inhibitory noradrenergic neurons that exerts a direct action on pressor 5-HT neurons.

Medullary serotonergic neurons also have been investigated by Chalmers et al. These investigators report that stimulation of the ventrolateral components of the B-1 and B-3 cell groups in the caudal medulla elevated blood pressure, while microinjection of methyldopa into this area had an opposite effect. Both actions were attenuated by 5,7-dihydroxytryptamine (5,7-DHT)-destruction of serotonergic neurons. Thus, reports to this symposium from the laboratories of Korner and Chalmers both identify a role for 5-HT tracts in cardiovascular regulation and in the action of methyldopa. The observations of Chalmers and associates that stimulation of B-1 and B-3 cells elevated blood pressure appear to differ from those of Cabot et al., who reported that medullary raphe stimulation inhibited SPNs.6 Raphe 5-hydroxytryptophan (5-HTP) neurons correspond to the B-1 cells of Dahlstrom and Fuxe.14

The information presented in this symposium and in the recent literature confirms the channeling of afferent baro- and chemoreceptor signals and other relevant information through the NTS and narrows the number of relevant descending tracts to the SPNs to about seven. Transmitters involved include norepinephrine, epinephrine, serotonin, and newly recognized roles for glutamate and GABA.

Of the neurotransmitters known to be involved in brain cardiovascular regulation, the catecholamines have been most intensively investigated because of the antihypertensive actions of the centrally acting a-adrenergic agonists.5, 20, 21 The exact role of catecholaminergic terminals in sites identified with baroreceptor responses,14, 16 (2) the prevention and reversal of sinoaortic denervation hypertension by i.c. 6-OHDA22 and NTS destruction,23, 24 (3) the production of hypertension by injection of 6-OHDA into the NTS,25 and (4) reduction in blood pressure by direct injection of norepinephrine into the NTS.26 Contrary evidence is the unchanged efficacy of clonidine in experimental animals whose CNS norepinephrine stores are depleted by treatment with reserpine and a-methyl-p-tyrosine.5, 20 There is little disagreement, however, that methyldopa, clonidine, and clonidine-like drugs act on central a-receptors. Thus, the molecular biology of catecholamine enzymes, neurons, and receptors were prominently addressed in this symposium.

Dr. Tong Joh reported that the enzymes that convert tyrosine to epinephrine share protein domains in their primary structures. Genetic analysis revealed evidence of gene homology for dopamine /-hydroxylase (DBH) and PNMT, which suggests that all catecholamine enzymes may be coded for by a single gene or by linked genes. A common ancestral gene is proposed.

Dr. Caron employed affinity chromatography and high performance liquid chromatography to purify /-adrenergic receptors. Antibodies raised against these receptors were used to localize /-adrenergic receptors to postsynaptic sites in discrete brain structures. Newly developed photoaffinity probes found that /,- and /,- receptors resided on peptides of similar molecular weight, whereas the a, probe bound to a considerably larger peptide.

Using radioligand binding with H-P-aminoclonidine (an a,-agonist) and H-rauwolscine (an a,-antagonist), U’Prichard (whose work will be reported separately) found that rat, bovine, and human brain /,- receptors behave similarly to those on human platelets. Brain /,- receptors exist as two interconvertible affinity states for agonist binding designated high (H) and low (L). Formation of the high-affinity state (H) appears to be a prerequisite for coupling of receptor to effector, presumably adenylate cyclase. Regions of the brain differ in a,-receptor densities and in high-low affinity states. Chronic agonist treatment down-regulates brain a,-receptors. Certain antagonists, such as yohimbine but not Rx 781094, up-regulate a,-receptors. These antagonists also differ in their high-low affinities, which may explain some of their different pharmacological properties. Both a,- and a,-receptors were found to be linked strongly to epinephrine rather than to norepinephrine in the brain stem and hypothalamus. Studies with inbred rat strains that differ in hypothalamic and brain stem PNMT activity demonstrated a specific inverse relationship between epinephrine and brain a-adrenergic receptors. This model may aid in the elucidation of the role of brain epinephrine in cardiovascular control.

It is clear that valuable tools are being developed for a better understanding of the sympathetic nervous system and the physiological and pharmacological interventions that affect it.
Pharmacology

A central theme of this symposium is the agonist effect of methyldopa, clonidine, and clonidine-like drugs on central α-receptors. This concept and its historical development were reviewed by Professor van Zwieten. Professor van Zwieten noted that clonidine and guanfacine reach the brain stem regulatory centers by virtue of their lipophilicity, whereas the amino acid methyldopa after brain penetration exerts its effects by conversion to active metabolite(s). All appear to stimulate the same inhibitory interneuron system, which reduces sympathetic tone and heart rate and lowers blood pressure. Activation of a cardiac presynaptic α-receptor may contribute to the bradycardia induced by clonidine. This group and others hold that the α-receptors responsible for the action of these drugs are located postsynaptically and that the sedation associated with their use is also α-mediated. It has been determined previously that clonidine and α-methylnorepinephrine are selective for α1-receptors and α2-receptors and that this selectivity applies to α-receptors in at least some appropriate brain centers.

The three drugs do differ relative to the withdrawal reaction. In a novel animal model developed by Thoolen et al., van Zwieten reported that clonidine exhibited a prominent hypersympathetic syndrome on withdrawal, guanfacine a modest one, and methyldopa little or none. The difference between clonidine and guanfacine can be explained on a kinetic basis: the largely different half-lives of the two drugs underlie a greatly different rate of elimination. The explanation for the difference between methyldopa and the other drugs is not available. Louis observed that clonidine is widely distributed in rat brain and has a major effect on centrally acting sympathetic activity and central a-receptors, respectively. The order of events for part explain the rebound phenomena. REM sleep is considered a sensitive indicator of changes in central noradrenergic activity and has been shown to be reduced by clonidine and guanfacine.

Changes in α1- and α2-receptors in response to methyldopa administration were investigated by Freed in normotensive and hypertensive rats. Methyldopa down-regulated α2-receptors in both animal models to similar degrees. α1-receptor levels, however, were higher in untreated Wistar-Kyoto (WKY) rats than in the spontaneously hypertensive rat (SHR) counterparts and were unchanged by methyldopa treatment. In contrast, α1-receptor concentrations increased in SHR after methyldopa administration as β2-receptors and blood pressure fell. Freed concluded that α1-receptor numbers may reflect central sympathetic activity and may mark responses to methyldopa.

The investigations reported by Louis suggest that α1-adrenergic receptors in brain, kidney, heart, and peripheral blood vessels differ sufficiently to permit the development of new highly selective agonists and radioligands.

The metabolite responsible for the central antihypertensive effect of methyldopa usually is identified as α-methylnorepinephrine or α-methyldopamine also has been proposed as the primary metabolite. This issue was investigated by Robertson et al., who reported that α-methylnorepinephrine was more potent than α-methylnorepinephrine or epinephrine in lowering blood pressure when injected into the cerebral ventricle or NTS of normotensive rats. The depressor effects of all three agonists could be attenuated with either the α-blocker yohimbine or the β-blocker timolol and could be abolished by combined blockade. Thus, α-methylnorepinephrine joins α-methylnorepinephrine (and α-methyldopamine) as an active metabolite of methyldopa.

Although centrally acting α1-agonists would be expected to affect any catecholaminergic neuron system, the brain stem structure most often mentioned as the principal site of action of these drugs is the NTS. This view is based on the following: (1) Heart rate and blood pressure are reduced when norepinephrine and methylnorepinephrine or clonidine or clonidine are microinjected into this center. (2) Clonidine reduces electrical potentials evoked in the NTS by carotid sinus nerve stimulation, an effect antagonized by yohimbine. (3) Localized cooling of the NTS increases sympathetic nervous system activity and abolishes the sympathoexcitatory and vagal effects of clonidine. (4) The time course of α-methylnorepinephrine accumulation and disappearance in the NTS after subcutaneous administration of methyldopa to rats correlates well with the hypotensive time course in this species. The current report by Louis that the NTS is probably the main site of action of methyldopa repeats the conclusion previously made by this laboratory. Attention is directed to other reports in this symposium and in the literature that note possible roles for the C-1 epinephrine tracts from the medulla (Reis et al.), pontine A-5 noradrenergic projections (Komer et al.), the B-1 and B-3-5 HT tracts from the medulla (Komer et al.; Chalmers et al.), the anterior hypothalamus, and the spinal cord.

Clinical Pharmacology

The clinical profiles of methyldopa and clonidine are well established and have been reviewed recently. Guanfacine, a recent introduction, appears to resemble clonidine in its clinical effects but has a longer duration of action. The investigations reported in this symposium have focused on certain clinical consequences of central sympathetic inhibitors.

Brown and colleagues employed plasma norepinephrine and growth hormone concentrations as indices of peripheral sympathetic activity and central α-receptor stimulation, respectively. The order of events after the intravenous administration of clonidine or guanfacine to normal volunteers were reductions in plasma norepinephrine concentrations, reductions in blood pressure, and elevations in growth hormone levels. The delayed rise in growth hormone suggests that the initial fall in plasma norepinephrine concentrations is a peripheral effect. This possibility was explored in rats with the selective α1-antagonist Rx 781094, intravenously and intracerebroventricularly (i.e.,) before administering intravenous bolus doses of clonidine.
Central α-receptor blockade inhibited the clonidine-induced reductions in blood pressure much more than the reductions in norepinephrine concentration, which tended to confirm the clinical observation. The 6-OHDA experiments in rabbits reported by Korner et al., suggest that approximately 30% of methyldopa-induced blood pressure reduction is due to biotransformation in peripheral sympathetic neurons.

Brown et al. confirmed previous observations in hypertensive patients, that central α-receptor agonists do not increase plasma growth hormone concentrations in patients with elevated blood pressure.

Reid and associates provided clinical confirmation of the relative incidence of the withdrawal reactions among clonidine, guanfacine, and methyldopa as described by van Zwieten in an animal model. A new approach to the management of this potentially dangerous situation is described. The proposal that the withdrawal reaction may result from down-regulation of α-adrenergic receptors is consistent with the observations reported by Freed.

Central inhibition of sympathetic tone has important hemodynamic and pathophysiological consequences, which have been reviewed by Frohlich. Blood pressure-lowering is brought about by reductions in peripheral vascular resistance and cardiac output without significant reflex increases in heart rate. Blood flow to vital organs is maintained. Attenuation of effect may occur as a result of volume expansion, thus these drugs are usually used as step-2 agents with a diuretic.

Reversal of left ventricular hypertrophy, a recognized risk factor in hypertension, is another beneficial consequence of this mode of antihypertensive therapy. Frohlich reports that methyldopa reduces cardiac mass in normotensive and hypertensive animals without loss of contractility. The functional reserve of the regressed heart currently is under investigation. Reversal of left ventricular hypertrophy in hypertensive patients with methyldopa has been reported by Fouad et al., who noted this effect could not be attributed to reduction in blood pressure alone. Frohlich was unable to demonstrate reduction in cardiac mass with clonidine at antihypertensive doses in his animal model. This apparent difference between methyldopa and clonidine is unexplained.

In the final paper, Professor Dollery reported on a 15-year follow-up study of 546 patients with moderate to severe hypertension, 205 of whom were treated with methyldopa. Survival at 10 years was 76% in men and 88% in women, gratifying figures in view of the initial severity of hypertension. Longevity of patients who were initially over 60 years of age was only slightly less than that of the general population. Patients under age 60 at presentation fared less well than the general population but much better than untreated patients of comparable severity. There were no drug-related deaths. As expected, mortality patterns reflected the initial severity of hypertension, shifting from renal failure, heart failure, and cerebral hemorrhage in the more severely affected patients, to myocardial and cerebral infarction in those with milder hypertension.

Acknowledgment

The author is grateful for the assistance of Mrs. Barbara Masten in the preparation of this manuscript.

References

8. Loewy AD, Gregorie EM, McKellar S, Baker RP. Electrophysiological evidence that the A5 catecholamine cell group is a vasomotor center. Brain Res 1978;181:421-449


33. De Jong W, Nijkamp FP. Centrally induced hypotension and bradycardia after administration of alpha-methylnoradrenaline into the area of the nucleus tractus solitarii of the rat. Br J Pharmacol 1976,58:593–598.


Money can't buy it. But a changed life-style can go a long way toward a healthier future.

Smart living includes eating right—the kinds of delicious, low-fat, low-cholesterol foods contained in the American Heart Association Cookbook. It's designed to help health-conscious people prepare foods that will help them maintain a reasonable weight, reduce the amount of fat and cholesterol in the diet, and cut salt intake.

In this fourth edition of the AHA Cookbook, you'll find the latest scientific evidence on the relationship between diet and heart health. You'll also find:

- Dietary guidelines for children—how you can start them off right with low-fat, low-cholesterol foods and still satisfy the needs of the "fast food" generation.
- A complete guide to restaurant dining
- A totally revised fat and cholesterol chart outlining the fat content of common foods
- Expanded information on the basics of microwave cookery

For a blend of good taste and good health, recommend the American Heart Association Cookbook to your patients.
In summary: satellite symposium on central alpha-adrenergic blood pressure regulating mechanisms.
W B Abrams

Hypertension. 1984;6:II87
doi: 10.1161/01.HYP.6.5_PT.2.II87

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/6/5_Pt_2/II87

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/