Brief Review

Peripheral Dopamine in Pathophysiology of Hypertension
Interaction With Aging and Lifestyle

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Dopamine, an ancestral catecholamine, is physiologically natriuretic and vasodilating, thus essentially protecting against hypertension. Its actions are overshadowed by the opposite effects of its main biological partner, norepinephrine, and this is accentuated with aging. Clinical observations combined with molecular biology approaches to catecholamine-synthesizing and catecholamine-metabolizing enzymes and receptors permit the identification of some inborn defects. Subtle changes in the dopamine–norepinephrine balance may account for the enhanced peripheral noradrenergic activity seen in the setting of decreased dopaminergic activity in advanced age. These changes may contribute to the diminished ability of the aged kidney to excrete a salt load, as well as to the finding that systolic blood pressure increases with age in populations with a high, but not in those with a low, intake of salt. The attainment of advanced age in Western societies with adverse lifestyle changes (mental rather than physical stress, excess salt intake, overeating, sedentarism) appears to facilitate the development of hypertension. The adaptation to all the preceding lifestyle changes necessitates an increased dopamine generation, which may initially compensate to maintain appropriate natriuresis and vasodilation since many patients with initial borderline essential hypertension express their sympathetic hyperfunction, in addition to increased norepinephrine release, by excessive dopamine release. However, the progression of hypertension is accompanied by a peripheral dopaminergic deficiency and diminished ability to excrete salt. This may represent an eventual inadequacy of a phylogenetically redundant system resulting in decreased natriuresis and vasodilation and may account for the responsiveness of established chronic hypertension to salt restriction, diuretics, and dopaminomimetic medication. (Hypertension 1991;18:709–721)

Over the last decade, it has become apparent that dopamine (DA) is an important neurotransmitter in the peripheral nervous system. Nonneuronal (kidney, intestine, blood vessels) and neuronal (neural terminals, adrenal medulla) tissues are target organs for circulating DA and also for DA synthesized and secreted locally as a paracrine substance. DA receptors located extracellularly in plasma-exposed cellular membranes transduce their signals to the intracellular milieu through a variety of second messengers, including adenylate cyclase, phospholipase C, protein kinase C, and other protein kinases. Peripheral DA_{1} receptors (typical for vascular smooth muscles and renal tubules) act via adenylate cyclase and phospholipase C stimulation, whereas DA_{2} receptors presynaptically suppress the release of norepinephrine (NE) via adenylate cyclase inhibition. DA has been shown to affect the actions of ion transporters as well as a variety of cellular enzymes and appears to be physiologically important in the control of renal function. The sum of the effects of physiological DA concentrations on the kidney (DA_{1}-mediated vasodilatation and natriuresis), vascular system (DA_{1}-direct vasodilatation and DA_{2}-mediated sympathoinhibition), and the adrenals (DA_{2}-mediated aldosterone suppressive action) results in a decrease of blood pressure (BP) via natriuresis and vasodilation. As such, DA is a serious candidate as a BP modulator, working in concert with other hypotensive and natriuretic agents such as prostaglandins, kal-likrein-kinin, and atrial natriuretic factor (ANF) but...
in opposition to hormones (NE, renin-angiotensin, aldosterone, endothelin) and serotonin, which act in the opposite direction, producing vasoconstriction and sodium retention. The DA/NE ratio, discussed later, is of particular biological significance, being closely linked to dopamine β-hydroxylase (DBH), a highly heritable enzyme.

The main cardiovascular DA₁ receptors relevant to BP regulation reside in blood vessels, particularly in the renal and mesenteric vessels where they were first discovered in renal tubules and in the juxtaglomerular cells. The stimulation of the receptors results in vasodilation, natriuresis, and renin release. DA₂ receptors are localized mainly on postganglionic sympathetic nerve terminals and in the adrenal cortex zona glomerulosa; inhibition of NE and aldosterone release is the main consequence of their stimulation. DA₂ receptors have, however, also been located on the intimal layer of the renal vasculature and in glomeruli where presynaptic DA₂ receptors do not mediate NE release. Intrarenal DA may also act at postsynaptic renal vascular or glomerular DA₁ binding sites resulting in a reduction in renal blood flow and decrease of sodium excretion. Sympathetic ganglia contain both DA₁ and DA₂ receptors. Although synaptic ganglionic NA receptors are probably distinct from vascular DA₂ receptors, the overall result of those receptor agonism appears to be an inhibition of neurotransmission. Thus, most evidence suggests that DA receptor stimulation results, with the exception of renin release and some intrarenal vascular DA₂-mediated actions, in an essentially antihypertensive effect through vasodilation, natriuresis, and inhibitory modulation of sympathetic activity. This effect has been well documented in studies using a series of specific DA₁ and DA₂ receptor agonists and antagonists. Of particular interest and homeostatic importance is the presence of DA₁ receptors in renal tubules, the stimulation of which produces diuresis and natriuresis. The origin of DA stimulating these receptors is, however, controversial. Because there is no direct evidence that renal DA-containing nerves have a functional effect on whole kidney hemodynamics or sodium handling, it is probable that the majority of DA homeostatically involved in renal hemodynamics and sodium handling is of nonneuronal origin. It has been suggested that salt loading activates the release of dihydroxyphenylalanine (DOPA) entering the kidney, and this DOPA may function as a prohormone and source of intrarenal DA generation. An alternative model of renal amine production in response to NaCl intake proposes that alterations in renal blood flow or renal tubular transport account, in a close interaction with renal serotonin generation, for the renal DA response to high NaCl intake. However, the regulation of DOPA uptake and decarboxylation and the release of DA from the proximal renal tubular cells, as well as renal tissue DA concentrations, are largely unknown. In addition to this renal effect of DA, natriuresis can also be promoted indirectly by DA₂ receptor stimulation, which induces a presynaptic suppression of NE release in nervous tissues and a tonic inhibition of aldosterone release in the adrenal zona glomerulosa.

Dopaminergic agonism thus results in a multiplicity of actions. The physiological importance of intrarenal DA as a cell-to-cell mediator of renal function becomes evident. Despite many controversies resulting from a difficult distinction between physiological and pharmacological actions, most of the evidence suggests that physiological activation of the dopaminergic system results in lowering of BP. However, its role in the pathogenesis of hypertension is still controversial. Studies have been based on mostly indirect evidence, such as the use of DA agonists or antagonists, or parallel measurements of hormones such as prolactin that are under dopaminergic inhibitory control. Direct measurements of free DA are still very difficult and of doubtful precision. Measurements of renal DA overflow (e.g., in response to mental stress) and of some indirect indexes of DA release such as DA sulfates and other DA metabolites may be an alternative and probably more accurate way of overcoming this difficulty. Because these aspects are covered in several recent reviews, this review will rather concentrate on recent findings on DA-releasing mechanisms, on the molecular biology of DA synthesis, metabolism, and action, and on a more general view of natriuretic substances as they relate to DA and hypertension.

Homeostatic Stimuli Involved in Dopamine Release and Inhibition

The well-known increase in catecholamine release in response to adrenergic nerve stimulation results from an activation of sympathetic neurons that is associated, in more generalized reactions, with an adrenomedullary discharge. Nerve impulses from preganglionic cholinergic neurons are involved in activation of the rate-limiting enzyme tyrosine hydroxylase (TH), which catalyzes tyrosine conversion to DOPA. High levels of the relatively nonspecific aromatic L-amino acid decarboxylase (AADC) rapidly decarboxylate DOPA to DA, which enters the chromaffin granules of sympathetic nerves and the adrenal medulla where it is converted by DBH to NE. The main mechanism of sympatoadrenomedullary activation by stress is the nerve impulse–mediated approximately threefold increase of TH activity and doubling of DBH. TH activity is thus mainly under neural control but is also partly dependent on glucocorticoids and neuropeptides such as secretin and vasoactive intestinal peptide, as demonstrated in sympathetic ganglia.

Although most stress-related catecholamine release studies concentrated on NE and epinephrine, some previous investigations have indicated that DA secretion may be predominant to a point, temporarily transforming noradrenergic into dopaminergic terminals. DA release may predominate when DBH activation (or the transvesicular transport of DA to the site of NE synthesis) does not keep pace with
Peripheral sympathetic nerve terminals and the adrenal medulla consists of a large temporary increase in the rate of tyrosine hydroxylase (TH) and L-amino acid decarboxylase (AADC) reactions and a variable but usually somewhat smaller increase in dopamine β-hydroxylase (DβH) and phenylethanolamine-N-methyltransferase (PNMT) reactions (represented by thick and intermediate arrows, respectively). This results in elevated concentrations of dihydroxyphenylalanine (DOPA) and DA relative to NE and epinephrine (E). The release of all the catecholamine neurohormones (DA, NE, and E) into the bloodstream is enhanced by strong sympathetic activation, but DA release may increase to a much greater extent than NE or E. Thus, peripheral sympathetic nerve terminals and the adrenal medulla may become partially "dopaminergic,"25,26 when activated by stress, exercise, or central abnormalities associated with essential hypertension. The inhibitory feedback loop on NE synthesis (B) is characterized by saline or colloid infusion-induced volume expansion leading to inhibition of DβH activity.29 This response may be complemented, as suggested in humans after high dietary salt intake, by stimulation of TH activity, which increases circulating DOPA concentrations serving as a prohormone for urinary DA generation.14 When both are combined, the result is elevated urinary DA and DOPA concentrations parallel to increased natriuresis. → Stimulation of a biosynthetic step; ↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓→
well as DA$_4$, DA$_5$, and DA$_3$ receptors were cloned; some of them were also chromosome-mapped (Table 1).

Of particular interest is a newly characterized renal inner medulla DA$_{3K}$ receptor subtype distinct from the DA$_2$ and DA$_3$ receptors, which may, by its location in the inner medulla, be involved in mediating the natriuretic/diuretic effect of DA. Most recently, brain DA$_{57}$ and DA$_{58}$ receptors were cloned. It is not yet clear whether and how the clozapine DA$_4$ receptor and the neuron-specific DA$_2$ receptor may relate to the function of specific brain and medullary BP regulating centers. Further subclassification is possible for enzymes of neuronal and nonneuronal origin as demonstrated in the case of DOPA decarboxylase (AADC). Different messenger RNAs (mRNAs) coding for AADC were found in tissues of neuronal and nonneuronal origin. This may be of interest as a possible explanation of a selective extraneuronal (e.g., kidney) AADC defect.

As the rate-limiting enzyme in catecholamine synthesis, TH is apparently of such vital importance that its absence is incompatible with life. D$eta$H deficiency rather exceptionally permits survival into adulthood but causes orthostatic hypotension. It is rarely recognized, but it provides a unique opportunity to determine the role of DA not only in this disorder but also in other forms of orthostatic hypotension. It also provides insight into the role played by DA in cardiovascular control in humans. In normal subjects, the presence of NE obscures the interpretation of any interventions aimed at modulating DA synthesis or action. In complete D$eta$H deficiency, increased endogenous DA is not only a simple marker of the enzyme's defect, but it is also a factor exerting a tonic BP-lowering effect, perhaps in relation to its vasodilatory or, possibly more importantly, its natriuretic properties.

A possible incomplete form of D$eta$H deficiency may be present in the familial dysautonomia with postural hypotension in children. Dopaminergic activity appears to predominate in laboratory tests of these children with subnormal excretion of NE metabolites, such as vanylmandelic acid and 3-methoxy-4-hydroxyphenylglycol, whereas DA metabolites, such as homovanillic acid, are elevated. In addition, D$eta$H is undetectable in a considerable proportion of these children. "Kinky hair disease" is another heritable trait with plasma free DA exceeding NE because of deficient dopamine $\beta$-hydroxylation. However, it is not clear whether this is an inherited absence of the D$eta$H enzyme or a copper deficiency leading to decreased D$eta$H activity.

MAO deficiency is of interest because of its incidence in men with X-chromosome deletion and the presence of clinical symptoms compatible with the cardiovascular actions of excess DA (rather than NE and epinephrine) such as hypotension and flushing. These symptoms as well as mental and sexual retardation, blindness, sleep disturbances, and social behavior disruption are also called Norrie disease. It is not clear to what degree these cardiovascular features of MAO A and B deficiency are due to excess DA, NE, and epinephrine escaping a part of their inactivation by MAO.

The characterization of DA$_{1}$, DA$_{2}$, and DA$_{3}$ receptors has greatly progressed recently. The recent cloning of a DA$_{2}$ rat receptor and a human and rat DA$_{1}$...
TABLE I. Molecular Biology of Some Dopamine-Related Enzymes and Receptors

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<td>?</td>
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</tr>
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<td>DA7 receptors</td>
<td>cDNA codes for 477 AA58</td>
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cDNA, complementary DNA; TH, tyrosine hydroxylase; AA, amino acids; DOPA, dihydroxyphenylalanine; mRNA, messenger RNA; AADC, aromatic l-amino acid decarboxylase; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; DA, dopamine; SHR, spontaneously hypertensive rats; NE, norepinephrine.

receptor41-43 may provide powerful new tools for the study of the role of these receptors in hypertension. It should be noted that these studies failed to show any expression of these specific mRNAs in the kidney. The strong pharmacological evidence of functional DA1 receptors in kidney2,12 would suggest the high likelihood that other subtypes of DA1 receptors different from those cloned in the central nervous system will be identified in the future. The DA3K subtype56 points in this direction. The most recent cloning of a novel DA545 and DA537 DA receptor may have detected new and more specific targets for neuroleptics, previously thought to interact only with DA2 receptors. The DA3 receptor may also be of importance in the periphery since a low level DA3 receptor mRNA was detected in the kidney. However, the DA2 and DA3 receptor signals are limited to the brain. The DA3 receptor mRNA is present in central dopaminergic regions. The fact that its affinity to DA is 10-fold higher than to DA2 receptor58 suggests that this system may be important for central dopaminergic tone.

These findings are of interest in relation to the described defective tubular DA1 adenylate cyclase coupling54 and vascular DA2-mediated feedback of NE release55 in spontaneously hypertensive rats (SHR). It is conceivable that some DA abnormalities relevant to hypertension may reflect primarily now-recognized DA receptor defects. These receptors may become a new target for more specific dopaminergic agonists and antagonists in the future.

Recognition of Dopaminergic Abnormalities

The main reason why the role of DA in hypertension and some syndromes such as DBH deficiency eluded recognition for so long is that most
research centers tend to measure only NE and epinephrine. This approach results from the paucity of free circulating DA, which is at the limit of detectability, while urinary DA, mostly originating from circulating DOPA entering the kidney, is considered to be a less reliable marker of dopaminergic activity. Newly emerging markers of dopaminergic release are DA sulfate, the most abundant circulating human catecholamine (77% of total catecholamines in human blood), and DA metabolites, such as 3,4-dihydroxyphenylacetic acid, homovanillic acid, and 3-methoxytyramine, the latter thought to reflect exocytotic DA release. The DA precursor, DOPA, also falls into this category because of its rapid and usually unimpeded decarboxylation to DA. Plasma DOPA has the added advantage of presently being, at least in humans, the best available marker of TH activity. These new markers and cyclic AMP (cAMP), the second messenger of DA, action, have expanded our understanding of the role of dopaminergic mechanisms in hypertension and offer new antihypertensive treatment approaches. The purpose of this review is to place DA, in view of what we know and should learn about it in the future, into the framework of evolution and of hypertension as a civilization disorder with details of available DA-targeted pharmacotherapy covered by some recent reviews.

**Dopamine as Part of the Balance Between Natriuretic and Antinatriuretic Factors**

The preceding description of the cardiovascular role of peripheral DA and of its genetic framework sets the stage for a broader physiological overview as it relates to the evolution of species, other natriuretic and vasodilator substances, the overall balance between natriuretic and antinatriuretic factors, and the effect of aging on dopaminergic activity.

The study of phylogenetic evolution within the animal kingdom suggests that the predominant catecholamine in fish was DA with ANF as a player for peptides. NE and epinephrine, as well as other hormones with antinatriuretic actions such as renin-angiotensin-aldosterone, appeared only later in reptiles, amphibians, and mammals during the transition from marine to terrestrial life. The role of NE and other antinatriuretic hormones was strengthened while that of DA and natriuretic substances was weakened when assuming an upright position became an evolutionary step associated with the need to maintain circulatory volume and BP during orthostatism. DA resembles other natriuretic hormones such as ANF, some prostaglandins, and kallikrein-kinin and appears to be, at least in the periphery, a phylogenetic "hangover," an odd catecholamine important for life in a high salt, marine environment. Under salt-poor terrestrial conditions and in higher mammals maintaining an upright position, when sodium retention and volume conservation become the main homeostatic concern, DA takes a backseat to NE and other sodium-retaining factors. This may explain why humans are so well equipped to survive with virtually no salt but cannot survive on salt water! The purpose of our inquiry is to understand when and by what mechanisms DA sometimes moves from the back to the forefront to participate in cardiovascular adaptation, possibly as a defense mechanism. Although such a response may appear to be phylogenetically regressive, it may be homeostatically beneficial as a balance against salt retention and vasoconstrictor mechanisms. Particularly with aging and progressive weakening of dopaminergic activity (as outlined below), decreased dopaminergic activity may be implicated in the pathogenesis of hypertension, cardiac failure, and edema, making it a possible target of DA-oriented pharmacotherapy.

As already alluded to, factors that are involved in maintaining the balance between natriuretic and antinatriuretic forces are linked, possibly in the form of a cascade, with both systems appearing to operate in a dynamic equilibrium. The interaction of DA with kallikrein-kinin, some prostaglandins, and serotonin seems to extend to ANF. DA is apparently a permissive factor for the action of this potent natriuretic hormone in the kidney. In addition, several prostaglandins also appear to be involved as regulators of cardiac ANF synthesis and secretion. Opposing these interacting natriuretic and vasodilating factors is a multiple-step vasoconstrictor and sodium-retaining system composed of NE, renin-angiotensin-aldosterone, serotonin, and probably also endothelin, which may be more or less linked together. The intrarenal interaction between the renin-angiotensin and dopaminergic (DA) systems seems to be particularly well demonstrated. For DA, the important homeostatic partner is NE. On the one hand, NE synthesis depends on its precursor DA, its access to vesicles, the site of DBH activity, and DBH activity itself. NE release depends on its presynaptic inhibition by DA. On the other hand, NE opposes all DA actions on vascular, renal (with the exception of renin release), and partly on adrenocortical targets.

**Effect of Aging on Dopaminergic Mechanisms**

Aging presents another level of complexity to our understanding of the role played by DA and by other catecholamines in the regulation of extracellular volume and blood pressure, as well as in the development of hypertension. In recent years, studies in aged human subjects free of disease have identified specific changes in fluid and salt homeostasis and in the regulation of vessel tone. There has also been a growing awareness of specific alterations in sympathetic nervous system function associated with normal aging. These considerations assume a great importance in the management of hypertension in view of the increasing numbers of individuals in Western societies who are reaching advanced age and are requiring medical care.

A large body of knowledge has been accumulated regarding age-related changes in the dopaminergic pathways in the central nervous system, yet very
little is known regarding the impact of age on the peripheral dopaminergic system. Many studies have documented increased basal plasma levels of NE in healthy elderly individuals,72,73 which appear to be due to increased plasma entry of NE into the bloodstream from sympathetic nerve terminals.73 It has been proposed that decreased baroreceptor sensitivity associated with aging and hypertension results in increased sympathetic nerve activity as demonstrated by nerve recording studies in healthy elderly subjects75 and, thus, in increased NE synthesis.

Although the impact of age on plasma DA levels has not been evaluated to this date, the urinary excretion of DA, the immediate precursor of NE, appears to decline by nearly 25% in healthy elderly individuals.76 Plasma levels of DOPA, the precursor of DA, also do not increase with age and may, in fact, decrease.77 The divergent changes in levels of NE and of its precursors, including DA, in aging cannot be reconciled on the basis of DβH activity alone. Although serum DβH activity has been reported to increase with age, no subjects over the age of 60 were examined in this study.78 Using the less reliable spectrophotometric determination of DβH, Annat et al79 found no difference in DβH levels between young and aged normotensive subjects.

Alternative explanations need to be proposed for these changes in DA and NE. Among others, these include the possibility that enzyme activities as measured in vitro may not be representative of in vivo enzyme activity, that these age-associated changes described may be tissue specific with some tissues making greater contributions to plasma catecholamine levels than others, or that the increased spill-over of NE into the bloodstream may be due in part to alterations in synaptic handling of NE with decreased reuptake of this neurotransmitter after its release.

In spite of the above differences, aging of both of these peripheral catecholamine systems appears to tilt the balance of their effects toward salt retention and increased vessel tone. A study performed with the dorsal hand vein technique has shown intact responsiveness of these vessels to α-adrenergic-mediated constriction with decreased responsiveness to β-adrenergic-mediated dilatation in healthy elderly subjects.71 These data, together with a growing body of receptor studies and with the finding of elevated plasma NE levels, suggest that the capacity of the peripheral noradrenergic system to affect vasoconstriction and salt retention is maintained and may even increase in aging. The number of DA₁ receptor subtypes was more than 50% lower in aged as opposed to young rats,80 and the stimulatory effect of DA on cAMP production was 40% lower in renal arteries from aged rabbits.81 The sum effect of all of these changes in the aging peripheral dopaminergic system could be to blunt the vasodilatory and natriuretic effects of DA, once again favoring salt retention and increased vessel tone.

However, the interaction of aging and salt balance is more complex when examined on the level of the whole organism. Both the ability to retain salt82 and the ability to excrete acute salt loads70,83 are impaired in older individuals. The former deficit in homeostatic balance appears to be more significant. To a large extent this reflects the greater contribution made to salt balance by the renin-aldosterone system and by thirst mechanisms, two systems whose function declines in aging,84,85 than by the renal catecholamine mechanisms discussed above.

A final consideration involves the observation that many of the changes described in the course of normal human aging or aging without identifiable disease involve heterogeneous patterns of change. It has been suggested that it may be possible and useful to separate normal human aging into two categories, usual and successful. Extrinsic factors such as diet, exercise, personal habits, and psychosocial habits appear to play a prominent role in the former category of aging.86

Renal aging provides an example of aging in which extrinsic factors may play a very prominent role. Although creatinine clearance has been shown to decrease with age in healthy humans, more recent data have shown great interindividual variability in renal function with advanced age.87 Some individuals exhibit major declines in renal function with age, whereas others do not show any significant change with age. Brenner's group88 has suggested that the protein-rich diet characteristic of Western societies could contribute to age-related losses of renal function. It has been shown that when systolic BP was compared in societies with low and with high salt intake, no difference was found between the 20–29- and 60–69-year-old groups in countries with low salt intake. Only in countries with high salt intake was BP significantly elevated in the older age group.89 It is possible that chronic salt ingestion contributes toward the development of hypertension in older age. It could also contribute toward the elevations of systolic BP associated with aging in some societies which have been characterized as falling within normal limits. In support of this hypothesis is the finding that older individuals appear to be more sensitive to the hypertensive effects of a 2-week course of salt loading.90 Thus, it is possible that many of the changes with aging, discussed above, and in renal effects of catecholamines favoring salt retention could contribute to this increased sensitivity. All of these factors will need to be considered in future studies of normal physiological aging of these systems. Such approaches lead to the hope that strategies will be devised to facilitate the transition toward aging with minimum deficits and disability.

Heterogeneity of Dopamine's Involvement in Essential Hypertension, a Disease of Civilization

Our present understanding of hypertension as a malady of modern civilization relates to maladaptation of humans, with atavistic homeostatic responses,
to modern lifestyles and more mental than physical threats. The well-coordinated somatomotor, visceromotor, and hormonal responses become dissociated when physical threats, to which humans are equipped by evolutionary heritage and "fight or flight" defense reactions, are replaced by more symbolic mental stress against which we are poorly adapted. There are fewer muscular (somatomotor) but more visceromotor (e.g., renal blood flow and cardiac output) and hormonal (e.g., catecholamines, peptides, and steroids) responses to mental stress, and these may contribute to diseases such as hypertension. This effect is amplified by modern lifestyle features such as excessive salt consumption, overeating, sedentarism, smoking, alcohol consumption, and others.

As far as autonomic nervous system reactions are concerned, NE release usually predominates and may account for sodium and fluid retention parallel to signs of sympathetic activation in response to physiological stress in young men at high risk for hypertension. During exposure to stressful stimuli and sympathetic activation with sodium retention, DA is coreleased with NE and may represent a factor balancing the consequences of the excessive NE release. In borderline hypertensive patients at a younger age, DA excretion is occasionally increased as part of the initial sympathetic discharge that characterizes this form of hypertension. Although plasma free DA is found to be normal (often undetectable) in most of these patients, there is evidence of elevated plasma DA sulfate, accelerated DA turnover, and enhanced exocytotic DA release as reflected by augmented urinary 3-methoxytyramine and homovanillic acid excretion. Initially, the generous DA response, occasionally even exceeding that of NE in some young borderline hypertensive patients, may be a beneficial antihypertensive defense balancing NE release and its consequences, such as vasocostriction and sodium retention. The natriuretic and vasodilatory component of the renal eicosanoid system, prostacyclin, also becomes hyperresponsive in borderline hypertension, but other components such as ANF remain normal. The degree to which DA and NE are released in response to adrenergic activation apparently depends on the access of DA to vesicles and on DβH activity. DβH activity has a great genetic and probably ethnic dependence, as has DA itself. Early hypertension is associated with hypernatriuresis, which may be, at least in part, mediated by DA release since it responds to DA antagonists.

The corresponding rat model of prehypertension or hypertension (SHR) reproduces these patterns of high DA turnover and excretion. This increase may be secondary to abnormal DA adenylate cyclase coupling in the tubules and to vascular DA2 presynaptic receptor abnormalities, the latter change resulting in a decreased ability of DA to inhibit vascular NE release in spontaneously hypertensive rats. An alternative mechanism of increased DA release may be the reduced DβH activity (as previously found relative to TH activity in the adrenals) in several tissues (adrenal, spleen, and heart ventricle) in the prehypertensive stage of this rat model at age 6 weeks. If we apply some of these findings to humans, it is conceivable that either incomplete DβH deficiency, decreased suppressibility of DβH and plasma NE by a high salt intake, or as previously observed in young hypertensive patients, a reduced serum DβH increase in response to standing and furosemide may accentuate DA synthesis at the expense of NE. Moreover, in a longitudinal study (over 5 years) with originally normotensive subjects, the BP elevation found in some of them was accompanied by decreased serum DβH activity. This suggests that some young borderline hypertensive patients are predisposed to a particular sympathetic discharge in which DA not only equals but, as we have seen in exceptional pseudopheochromocytoma patients, even exceeds NE release. For evident genetic or ethnic reasons, these patterns of catecholamine responses in early hypertensive patients are not necessarily universal. As observed in Japan, some early borderline hypertensive patients may not go through this phase and even in the prehypertensive stage may rather exhibit a dopaminergic deficiency. The ethnic factor, applicable particularly in North America to the black population, appears to be an important determinant of DA's participation in the sympathetic discharge at the point where the hypertensive process begins.

The markers of dopaminergic activity appear to be more homogeneous in advanced stable hypertension. The development of hypertension is usually a slow process, in which aging may attenuate the baroreceptor-mediated inhibition of NE release. This may be related to a progressive decline of dopaminergic activity with deficient renal DA and natriuretic responses to salt loading and diuretics, and possibly also a diminished decarboxylation of DOPA to DA as suggested by exogenous DOPA administration (Figure 3) indicating a reduced DA turnover. These patterns are typical of low renin essential hypertension, a form of stable hypertension of long duration. This form of hypertension, usually affecting the older age group and black patients, appears to be one in which the age-dependent decline in DA and vulnerability to salt are accentuated. It becomes a form of hypertension that is beneficially responsive to diuretics and dopaminomimetic agents. The impaired intrarenal DA production after saline in diabetics, even if normotensive, may contribute to their propensity to become hypertensive.

Hypertension is one of the most common medical diagnoses in elderly patients. Because the physiological alterations associated with hypertension are superimposed on other physiological changes taking place in the course of normal aging, it is necessary to take the latter factors into account in the management of hypertension in the elderly. Furthermore, some of the physiological changes that have been...
acute high sodium intake, reflects a racial difference in the ability to preferentially use DA or ANF, helps us to cope with excess salt.

The two main known antihypertensive factors thatmans, albeit more as a reaction to chronic than to their hypertension. It will be interesting to explore whether ANF hyporesponsiveness to salt in some white hypertension-prone humans, albeit more as a reaction to chronic than to acute high sodium intake, reflects a racial difference in the ability to preferentially use DA or ANF, the two main known antihypertensive factors that help us to cope with excess salt.

Among the civilization factors recognized as possible contributors to hypertension, there are some in which even DA adjustment itself may be insufficient to adapt this ancestral catecholamine to the homeostatic needs of modern life. The excessive dietary sodium intake of modern societies, compared with the negligible salt intake of their ancestors, may require a more powerful compensatory mechanism than that with which humans are equipped by their evolutionary and genetic heritage. The sodium retention characteristic of non-modulating hypertension, which appears to represent a genetic trait, reflects a reduction in intrarenal dopamine production in response to a sodium load. American blacks are typical hypertension-prone subjects; even before becoming hypertensive, they have been found to have a relative deficiency in acute DA responsiveness to salt, and their ANF response appears later, apparently as a reaction to their hypertension. It will be interesting to explore whether ANF hyporesponsiveness to salt in some white hypertension-prone humans, albeit more as a reaction to chronic than to acute high sodium intake, reflects a racial difference in the ability to preferentially use DA or ANF, the two main known antihypertensive factors that help us to cope with excess salt.

The potential role of DA in another lifestyle change, overeating, is also interesting. Caloric and particularly high protein intake, characteristic of modern Western society, provokes postprandial natriuresis. It has recently been demonstrated by suppressing the extraneuronal generation of DA from DOPA, which probably occurs in the proximal tubular cells, with an AADC inhibitor that DA plays an essential role in provoking this form of natriuresis. Two preliminary reports suggest that this adaptive response is insufficient in older normotensive and hypertensive subjects. If eating in excess of our energy output is a feature of modern Western societies, it is conceivable that the cumulative effect of insufficient postprandial natriuresis due to a relative decline in peripheral dopaminergic system activity with aging and the hypertensive process itself may have a compound influence in producing hypertension so often linked to obesity. The well-known decrease of BP with dietary restriction and weight loss may well relate to a reestablishment of the balance between the need for postprandial natriuresis and the ability to stimulate DA generation in response to food. The DA deficiency in obese hypertensive patients may be an interesting pointer in this direction. We have previously noted (unpublished observations) that obese patients with idiopathic edema, a condition with deficient DA responses to salt loading, have a very low caloric ceiling (between 500 and 700 cal/day or 2,100 and 2,940 J/day) below which they are able to avoid sodium retention. However, whenever their intake exceeds this ceiling, a positive salt balance and edema become unavoidable.

Finally, one of the most typical features of civilization is the lack of physical exercise and sedentarism. It has long been known that DA is activated after physical exercise. For this reason, urinary DA has been used as an index of the level of training and reserves of the sympathoadrenal system in athletes and of adaptation to stressful environments. Higher baseline DA sulfate concentrations have been reported in the plasma of well-trained than in that of less well-trained long distance runners and dogs. Increased sympathoadrenal DA release is more likely to accompany subacute or repeated stress associated with a sense of effort or actual physical work than acute stress associated with distress and little physical work. This may be related to the primary association of effort with the sympathoadrenomedullary response while distress (followed by glucocorticoid stimulation altering the activities of catecholamine-synthesizing and catecholamine-degrading enzymes) appears to be linked to pituitary-adrenocortical activation. It is interesting that after aerobic exercise, there is a reduction in NE with an increase in DA and that the exercise-related decrease of BP and total peripheral resistance is attributed to this change. In general, subjects performing regular exercise have higher indexes of dopaminergic activity than untrained sedentary subjects. It is not clear to
what degree these findings depend on changes of DA and its sulfoconjugation. Some studies suggest, on the basis of free and conjugated catecholamine measurements in plasma and erythrocytes, that the mechanisms regulating sulfoconjugation may be altered in labile hypertension.125

It is thus conceivable that dopaminergic mechanisms initially activated in response to stress and some lifestyle changes may also become, if inadequate in the long run, culprits of faulty adaptation to some features typical of modern society such as excessive salt consumption, overeating, and sedentarism. To what degree this initial adaptation succeeds and organismal function is maintained during the course of aging may depend on a variety of genetic and ethnic factors.

Against this evolutionary background of species and individuals, genetically hypertension-prone humans can be expected to have a particular facility to stimulate sympathetic nervous activity as part of their "defense response."24 Although the prohypertensive action of NE is indisputable, the role of DA as part of the defense against hypertension probably depends on the level of adrenergic tone and on the individual's genetic coding of enzymes important for DA synthesis, metabolism, and action. As discussed, with the progression of hypertension, adaptive dopaminergic activation may progressively weaken126 and make humans more vulnerable to other prohypertensive factors such as salt retention, overeating, or sedentarism, particularly subjects not sufficiently adapted by training. Since normal daily activities are punctuated by stimuli for peripheral sympathetic nervous activity (feeding, physical effort, and psychological stress), it is possible that a prolonged or more sustained response in the elderly induces a hyper-adrenergic state, even under "normal" circumstances,72 particularly in hypertension. It remains to be investigated to what degree a central dopaminergic deficiency,127 complementary to that in peripheral dopaminergic mechanisms, may be involved in the pathogenesis of hypertension and in the interaction with other natriuretic and vasodilatory factors to overcome these evolutionary odds. Given the well-known neurotransmitter role of DA in emotional and psychosocial interactions, clarification of this relation may represent an important contribution to our understanding as to why hypertension has emerged as such an important health problem at a time of spectacular industrial progress and human life extension when insecurity and psychosocial stimulation by suppressed anger128 have replaced the physical stress to which primitive humans were exposed.91 It may take time for the human race to adapt to these revolutionary changes.

While keeping this conflicting situation in mind we have to strengthen, in the prevention of hypertension, all elements that help to overcome these odds by adjusting our lifestyle. As some evidence suggests, this may, in the case of DA, take the form of a positive conditioning of dopaminergic mechanisms by exercise training. In contrast to some recent "salt liberation" advocates, we should postulate dietary salt limitations to decrease the demand for adaptive dopaminergic responses and to control obesity by an overall caloric and protein intake not exceeding our physiological needs. Education to introduce these lifestyle changes should start at a young age since with aging these measures may potentially lose their efficacy in preventing or slowing the progression of hypertension.

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