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Sympathochromaffin System Activity in the Elderly

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The sympathochromaffin system is composed of the sympathetic nervous system (SNS) and the adrenal medullae.[1] This system plays a key role to mediate internal adaptation to changes in the external environment, thus maintaining essential body functions such as blood pressure, body temperature, and fuel metabolism within a narrow range. There is evidence of impaired regulation of blood pressure, body temperature, and carbohydrate metabolism in the elderly.[2–5] Thus, there has been considerable interest in understanding the effect of aging on function of the sympathochromaffin system. The purpose of this paper is to review and discuss recent observations regarding the study of sympathochromaffin system activity in human aging, as assessed by measurement of plasma catecholamine levels and calculation of kinetic indices of catecholamine metabolism.

PHYSIOLOGY OF THE SYMPATHOCHROMAFFIN SYSTEM

Norepinephrine (NE) is the major neurohumoral messenger mediating SNS effects, while epinephrine (E) is the major catecholamine released by the adrenal medullae[6] (Figure 1). Specific sensitive assays have made it possible to measure plasma NE and E levels under a variety of conditions.[7–10] These studies have provided useful information about sympathochromaffin system activity in humans.[11] However, the level of catecholamine in plasma is the result of at least two dynamic processes: appearance into, and clearance from, the circulation.[12]

Norepinephrine in the circulation is derived mainly from "spillover" of NE released from postganglionic sympathetic nerve terminals.[13] Following its release into the neuroeffector junction of sympathetic nerve synapses, most of the NE is removed from that site by reuptake ($uptake_1$; neuronal removal) into the presynaptic nerve terminals. Some of the released NE escapes this process and is removed by $uptake_2$ (nonneuronal removal). Finally, a small fraction of NE in the neuroeffector junction spills over into the circulation (Figure 1). Plasma NE is, therefore, an indirect measure of SNS outflow. In contrast, the adrenal gland is the major source of circulating E. Epinephrine is released directly into the circulation from the adrenal medullae and transported via the circulation to its target cells (Figure 1). $Uptake_1$ is more important for inactivation of NE than E, while $uptake_2$ appears to be the major mechanism for inactivation of circulating E.[14,15] The plasma E level provides a direct measure of chromaffin tissue activity, including the adrenal medullae, under normal physiologic conditions.[1]

PLASMA CATECHOLAMINES IN THE ELDERLY

Plasma Norepinephrine Levels Investigations from several laboratories have confirmed that plasma NE levels at rest are significantly higher in older individuals.[16–18] Under appropriate conditions, increases in plasma NE levels appear to provide a sensitive and useful index of sympathetic neuronal function.[19] Thus, the higher plasma NE levels in older individuals suggest that SNS activity is increased in the elderly. The correlation observed between plasma NE and direct recording of muscle sympathetic nerve activity in humans[20] further supports this hypothesis.

In addition to the age-related increase of plasma NE in the supine resting state, as shown in Figure 2, plasma NE levels are elevated in the elderly throughout the 24-hour diurnal rhythm.[21] Several physiologic maneuvers elicit a heightened plasma NE response

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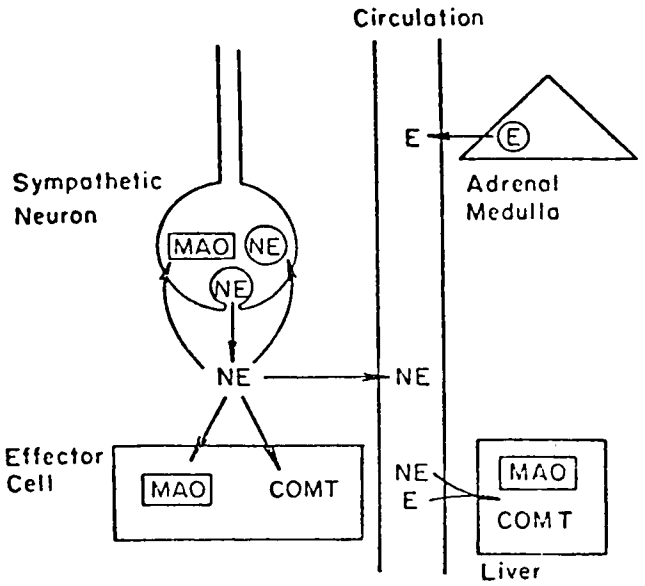

FIGURE 1. *Sources of circulating catecholamines. Norepinephrine (NE) is released from postganglionic sympathetic neurons into the synaptic cleft from where the majority is taken back up into the neuron and either stored in granules or metabolized by monoamine oxidase (MAO). Some of the remaining NE is enzymatically degraded by MAO and catechol-O-methyltransferase (COMT) locally and only a small fraction spills over into the circulation. Epinephrine is released from the adrenal medullae directly into the circulation and the majority is removed from the circulation.*

in humans.[10] There is evidence that plasma NE responses are significantly higher in older individuals during mental stress,[22] upright posture,[23] isometric exercise,[24] glucose administration,[23] and sodium restriction.[25]

Plasma Epinephrine Levels Despite the consistent findings of increased plasma NE with advancing age both at rest and during SNS activation, no age differences have been reported for plasma E. Plasma E levels are similar in healthy elderly and young subjects throughout the day.[21,22] In addition, the plasma E response to a mental stress test is identical in elderly and young participants.[22]

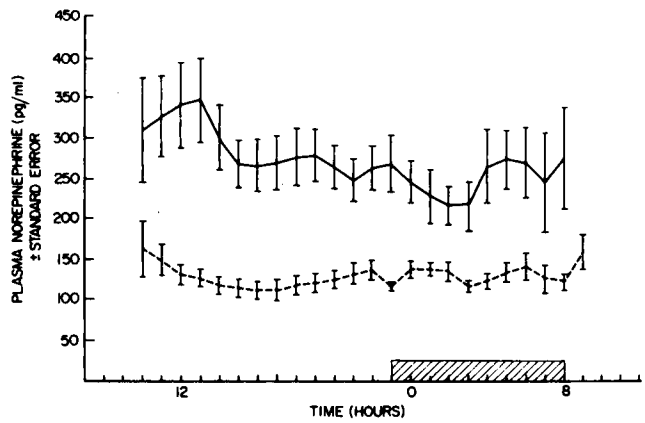

FIGURE 2. *Plasma norepinephrine (NE) concentrations over a normal undisturbed 24-hr period in 8 old and 10 young men. Plasma NE is higher in the old throughout the day, including the time during sleep (hatched box).*[21] —— *= aged normals (N = 8);* --- *= young normals (N = 10).*

CATECHOLAMINE KINETICS IN THE ASSESSMENT OF SYMPATHOCHROMAFFIN SYSTEM ACTIVITY

Infusion of Nonradiolabelled Catecholamines In this method NE or E is infused at a constant rate until a plateau plasma level is achieved.[26] Clearance (L/min) is calculated using the following equation:

$$\text{Clearance} = \text{infusion rate}/(\text{plateau plasma level} - \text{basal level}). \quad \text{(Eq. 1)}$$

Calculation of catecholamine clearance rate allows estimation of the rate of catecholamine appearance into the circulation (CA_{AR}) using the following equation:

$$CA_{AR} = \text{CA clearance} \times \text{basal CA concentration}. \quad \text{(Eq. 2)}$$

This method is based on three major assumptions. First, it assumes that steady state conditions have been achieved. Second, the infusion of exogenous catecholamine must not influence the appearance or clearance of endogenous catecholamine. Third, the method assumes that the kinetics of distribution and metabolism of the catecholamine systems can be represented by a single-compartment model, ie, all de novo sources of catecholamine enter into, and all irreversible losses leave from, the accessible (sampled) compartment.

This technique has been used in only two studies addressing NE kinetics with aging. Young et al.[23] found no significant change in NE clearance rate in five elderly participants compared to five young controls. Rubin et al.[27] studied eight young and eight elderly participants and found that NE clearance rate was unchanged in the elderly whereas NE appearance rate was significantly increased in this group both in the supine position and during upright posture.

Infusion of Radiolabelled Catecholamines The major assumptions underlying this approach are the same as those for the nonradiolabelled catecholamine infusion technique.[26] However, because tracer doses of catecholamines are used, it is very likely that this method does not disturb endogenous NE management. The rates employed during infusion of radiolabelled NE are 25 to 50 times < a NE infusion rate previously shown to have no effect on blood pressure and other metabolic parameters,[28] and they are 16 times < a NE infusion rate previously shown to cause

an increment of 3.0 pg/mL in plasma NE levels.[29] The radiolabelled NE infusion approach allows calculation of NE appearance rate (NE_{AR}) into, and NE clearance (NE_{CL}) rate from, the circulation based on the following mathematical relationships:

$$NE_{AR} = \frac{^3\text{H-NE infusion rate (dpm/mL)}}{\text{Specific activity of Plasma NE (dpm/pg)}} \quad \text{(Eq. 3)}$$

and

$$NE_{CL} = \frac{^3\text{H-NE infusion rate (dpm/mL)}}{\text{Steady state plasma } (^3\text{H-NE [dpm/mL]}).} \quad \text{(Eq. 4)}$$

Using this approach, Esler et al.[30] studied 34 healthy people ages 20 to 69 years of age and found a significant 30% reduction in NE_{CL} and an nonsignificant 14% increase in NE_{AR} in the elderly. In contrast, Hoeldtke and Cilmi[31] studied 13 elderly and 14 young participants and found that NE_{AR} is increased with advancing age while NE_{CL} is not significantly reduced. In addition, they used a complex urinary catecholamine metabolite excretion technique[32] combined with the ^{3}H-NE infusion method, correcting for estimated contributions due to brain and adrenal catecholamine excretion, to estimate total NE secretion by peripheral sympathetic nerves. Using this technique they reported that peripheral NE secretion is not increased in the elderly.

In the largest study to date (25 young and 18 elderly subjects) addressing the question of whether increased plasma NE levels in the elderly are due to increased NE_{AR} or decreased NE_{CL}, or a combination of both factors, we found both increased NE_{AR} and decreased NE_{CL} in the elderly.[33] These findings are illustrated in Figures 3 and 4. Because either the increased NE_{AR} or decreased NE_{CL} could contribute to the age-related elevation of plasma NE, forward-stepwise multiple linear regression analysis and partial correlations were used to determine which of the two was the more important determinant. The linear model, $NE = 197 + 717(NE_{AR}) - 129\ (NE_{CL})$, revealed that NE_{AR} and NE_{CL} explained 80% of the variance in plasma NE levels. Partial correlations showed that NE_{AR} alone accounted for 57% and NE_{CL} contributed 14% indicating that NE_{AR} is the more important determinant.

A subsequent study explored the possibility that diminished α-2 adrenergic inhibition of SNS outflow might account for the elevation of plasma NE and plasma NE appearance rate observed in older individuals.[34] If the increased plasma NE appearance rate in the elderly is due to a primary defect or loss of inhibitory α-2 receptors, this should be associated with an attenuated response to the α-2 adrenergic receptor agonist clonidine in the older subjects. However, clonidine was found to suppress plasma NE and NE appearance rate equally in young and older subjects, which suggests that the α-2 adrenergic mechanisms regulating SNS activity are functionally intact in older individuals.

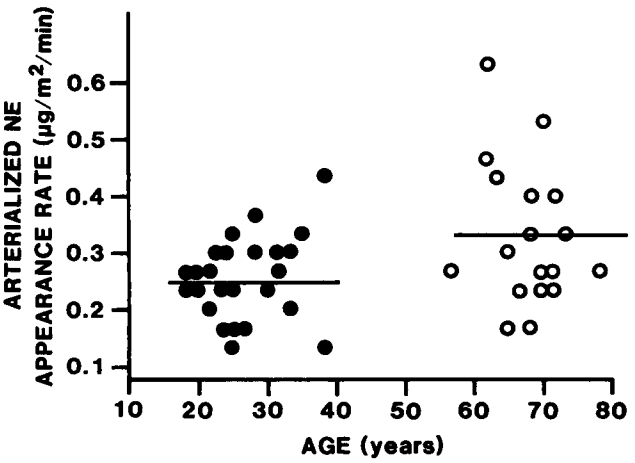

FIGURE 3. *Arterialized plasma norepinephrine (NE) appearance rate during ^3H = NE infusion for young (●) and old (○) adults. The values of the old averaged 30% higher than those of the young.*[33] $P < 0.016$.

Epinephrine Kinetics The basic analytic theory for calculation of clearance and appearance rates (see above) applies equally to the study of E kinetics. The nonradiolabeled E infusion technique has been used to compare the pattern of change in plasma E in young and elderly subjects. Wilkie et al.[35] found that lower plasma E levels were achieved by E infusion in the elderly participants. As a result, values calculated for E clearance were significantly higher in old than young

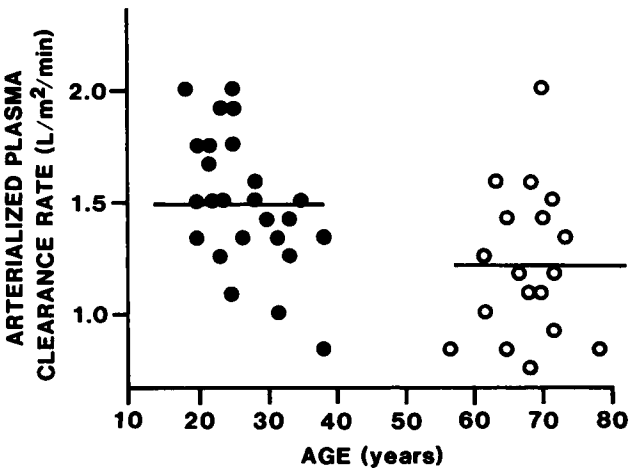

FIGURE 4. *Arterialized plasma norepinephrine (NE) clearance rate during ^3H = NE infusion for young (●) and old (○) adults. The values of the old averaged 14% lower than those of the young.*[33] $P < 0.006$.

subjects. More recently, we have reported the results of preliminary studies of E kinetics using radiolabelled E.[36] Basal E appearance rate was not significantly different in old and young, but E clearance was increased in the elderly, confirming the earlier findings with unlabelled E infusion. The findings suggesting increased E clearance in the elderly appear paradoxical, since NE clearance is diminished in the elderly. NE and E are removed by both uptake$_1$ and uptake$_2$ mechanisms. Furthermore, in young subjects the clearance rate of NE and E are virtually identical.[37] These findings imply a differential effect of age on a catecholamine removal mechanism that has a greater affinity for NE than for E.

PHYSIOLOGICAL IMPLICATIONS

What is the physiological, pathophysiological, and clinical significance of altered sympathochromaffin system activity with aging? Arterial blood pressure has been observed to increase as a function of age in humans, both in cross-sectional and longitudinal studies.[2] Increased SNS activity with resulting cardiac stimulation and vasoconstriction is a potential mechanism for such age-related increases of blood pressure, although blood pressure regulation is a complex process involving a number of neuroendocrine systems in addition to the SNS.[38] Although supine blood pressure tends to increase with age, orthostatic hypotension has also been reported to be a problem among older people.[39,40] The paradoxical findings of both increased blood pressure and orthostatic hypotension in the elderly raise the possibility of an age-related impairment of the baroreceptor mechanism which controls SNS input to the cardiovascular system. Such a possible age-related impairment of regulation of SNS control of arterial blood pressure would be of particular importance in the many elderly individuals who have medical problems which involve use of therapeutic regimens which can affect SNS activity (eg, diuretics, adrenergic blocking agents, antidepressant drugs, tranquilizers).

Pfeifer et al.[18] found decreased respiratory heart rate variability in the elderly, providing evidence for decreased parasympathetic nervous system (PNS) input to the heart. Because plasma NE levels were higher in the elderly, increased SNS input to the heart was postulated. One potential mechanism for such a link of increased SNS and decreased PNS activity is via the baroreceptor signaling mechanism, since a decline of arterial blood pressure normally results in simultaneous baroreceptor mediated increases of SNS and decreases of PNS activity. Since blood pressure in these elderly subjects was higher, not lower than in young people, a defective baroreceptor signaling mechanism and/or defective central nervous system processing of baroreceptor signals was hypothesized.

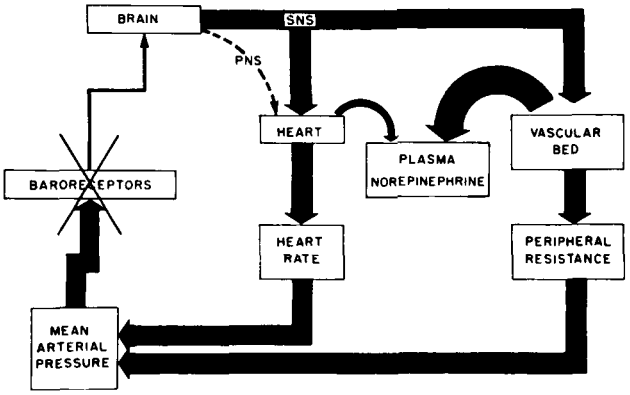

FIGURE 5. *Model of compensated autonomic nervous system regulation of the cardiovascular system in response to baroreceptor dysfunction. In this hypothetical model, an impairment of baroreceptor sensitivity, afferent neural transmission, or central processing of the brain initially results in central perception of low blood pressure. To compensate, cardiac and vascular sympathetic nervous system (SNS) activity increases and cardiac parasympathetic nervous system (PNS) activity decreases. These responses result in a compensatory increase in blood pressure, which stimulates the impaired baroreceptor system sufficiently so that the central nervous system perceives that the blood pressure has normalized.*[18]

As illustrated in Figure 5, such a defect could explain the findings of an age-related increase of blood pressure associated with increased SNS activity and decreased PNS activity. Similarly, Rowe and Troen[17] and Christensen[41] have suggested that the increases of plasma NE levels with aging may be due in part to impaired baroreceptor sensitivity.

Alternatively, the high NE levels in the elderly could represent a physiologic response to decreased cellular responsiveness to catecholamines. Evidence for an age-related impairment of tissue responsiveness to catecholamines, particularly to β-adrenergic receptor stimulation, has recently been reviewed.[42] However, an age-related increase of plasma NE levels to compensate for impaired adrenergic mechanisms cannot explain the observed elevated arterial blood pressure in the elderly. Since increased exposure to catecholamines can result in desensitization of adrenergic receptor function,[43] it is perhaps more likely that the age-related change in adrenergic receptors is secondary to the increase of NE levels.

If such a hypothesized baroreceptor signaling mechanism defect in the elderly exists, the increase of SNS activity may be specific for the cardiovascular system. For example, Pfeifer et al.[18] also found evidence that SNS input to the iris is not increased in the elderly. In addition, adrenal medullary activity as measured by both plasma E levels and nonradiolabelled and radiolabelled E kinetic indices, is not increased in the elderly.[35-37] These organs are not heav-

ily influenced by alterations of baroreceptor function. Thus it is possible that an impaired baroreceptor mechanism leads to a selective compensatory increase of cardiovascular SNS activity in the elderly.

SUMMARY AND FUTURE DIRECTIONS

Current findings indicate that aging in humans is associated with increased circulating levels of NE, primarily due to increased spillover of NE into the circulation. Current work has focused on plasma NE levels and the kinetics of circulating NE. However, the concept of a single compartment for NE is not in accord with the known physiology of NE metabolism which includes NE removal from the synaptic cleft by neuronal and nonneuronal mechanisms, and spillover of NE only secondarily from the synaptic cleft into the circulation. Thus, of more physiologic importance, are the kinetics of NE release and removal from the extravascular sites at which NE is released. Recent work indicates that a physiologically based two-compartment differential equation model can reproducibly predict the kinetics of distribution and metabolism of both NE and E.[44,45] The use of the powerful tools of computer assisted mathematical modeling[46,47] may allow quantitative estimation of catecholamine kinetics in the inaccessible sites of distribution and metabolism of the catecholamines, and provide further insight into the regulation of sympathochromaffin system function with aging.

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