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# Perspectives in Diabetes

## Chronic Sympathetic Activation

### Consequence and Cause of Age-Associated Obesity?

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**Primary aging in adult humans is associated with a progressive, tonic activation of the peripheral sympathetic nervous system (SNS). The purpose of this SNS activation and its physiological impact are, however, unknown. We hypothesize that the chronic stimulation of the SNS with aging is driven in part by a progressive accumulation of body fat. This “error” is sensed by the central nervous system via increases in adiposity-sensitive humoral signals (e.g., leptin, insulin) that cross the blood-brain barrier, activate subcortical areas involved in the regulation of energy balance (e.g., ventromedial hypothalamus), and stimulate SNS outflow to peripheral tissues. The SNS activation is intended to increase  $\beta$ -adrenergic thermogenesis in order to expend excess energy as heat rather than by storage of fat. Recent evidence, however, indicates that these adjustments are not effective in augmenting energy expenditure with aging. Indeed, older sedentary adults demonstrate reduced, not increased,  $\beta$ -adrenergic stimulation of metabolic rate because of reduced tissue responsiveness, presumably mediated by SNS-induced impairment of  $\beta$ -adrenergic signaling. As a result, age-associated SNS activation, initiated as a consequence of accumulating adiposity with the intent of preventing further fat storage, ironically, may in time evolve into a potential mechanism contributing to the development of obesity with aging. *Diabetes* 53:276–284, 2004**

**T**he sympathetic nervous system (SNS) is an essential tool for the central nervous system (CNS) in achieving its regulatory goal of maintaining organismic homeostasis. CNS-mediated SNS activation is produced during short-term changes in the physiological state (acute exercise, assumption of the upright posture) as well as in response to chronic pathological disorders (congestive heart failure, essential hypertension). During such conditions typically both the purpose (teleology) and the physiological impact (failure

or success in producing the intended effect) of the SNS activation are readily apparent.

It has been recognized for over 25 years that the SNS becomes progressively activated with increasing age in adult humans, independent of development of clinical disease (1,2). Yet, after more than a quarter of a century of investigating the specific changes that occur in SNS function with human aging, we still have no clear understanding of what this age-associated SNS activation is intended to accomplish or its physiological (or pathophysiological) consequences.

Our laboratory has been studying the effects of adult aging on the human SNS for more than a decade (2–11). In the present discussion, we first advance a unified working hypothesis addressing the question of why the SNS becomes tonically and progressively activated with aging. We approach this key issue from the standpoint that the chronic increase in SNS activity with aging is somehow intended to preserve homeostasis. We then address the important question of whether the SNS activation produced by this action is effective in accomplishing its regulatory goal.

We propose (Fig. 1) that the progressive SNS activation with human aging is, at least in part, in response to age-associated increases in adiposity. This increase in body fatness with age would produce elevations in putative “adiposity signals” (12,13) such as circulating concentrations of insulin and leptin, which cross the blood-brain barrier and bind to their receptor complexes in hypothalamic nuclei involved in the regulation of energy balance. This would, in turn, trigger an increase in SNS outflow to the peripheral tissues with the intention of stimulating  $\beta$ -adrenergic thermogenesis (i.e., expenditure of energy as heat) to prevent further storage of excess energy as fat. We further propose that, although this response is physiologically appropriate at least initially, ultimately it fails to achieve its regulatory goal of stimulating thermogenesis because the sustained SNS activation results in desensitization of the  $\beta$ -adrenergic signaling pathway. Indeed, we believe that this  $\beta$ -adrenergic desensitization actually serves to impair both basal and acute energy intake-evoked thermogenesis, thus ironically increasing the susceptibility of the aging adult to additional fat storage and future weight gain. As a result, a chronic activation of the SNS initiated by the CNS to prevent obesity may evolve with time into a mechanism by which the development of obesity is not only preserved but, perhaps, facilitated.

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CNS, central nervous system; MSNA, muscle sympathetic nerve activity; PNE, plasma norepinephrine; RMR, resting metabolic rate; SNS, sympathetic nervous system; TEF, thermic effect of food.

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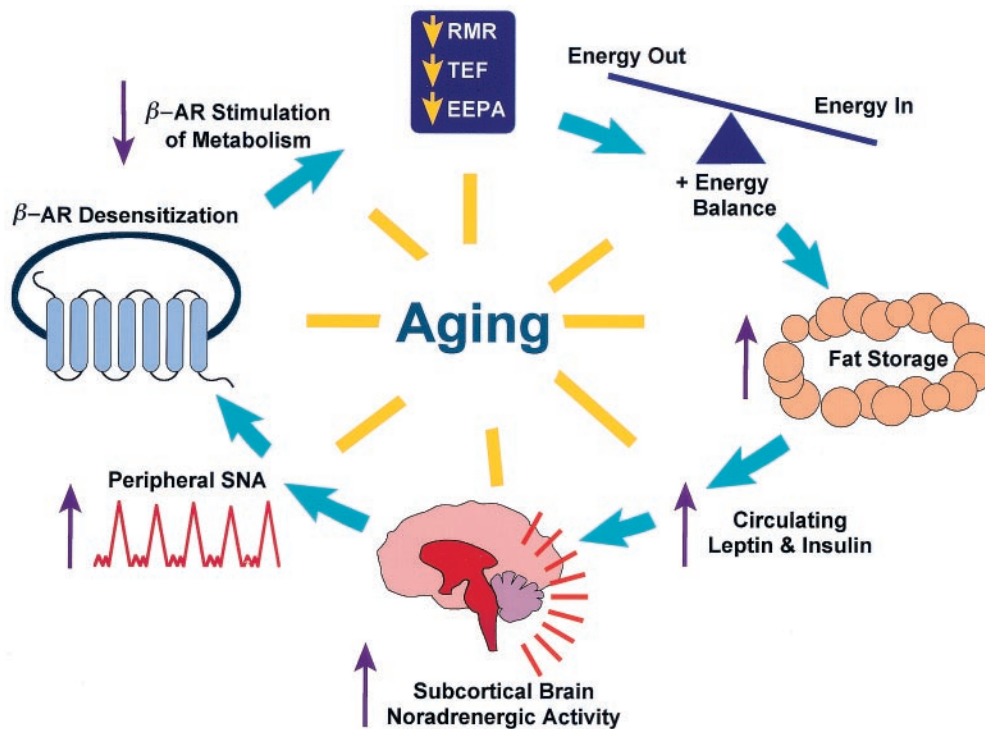


FIG. 1. Integrated working hypothesis explaining the effects of primary adult aging on peripheral SNS activity and its modulation of energy expenditure in humans. The chronic stimulation of the SNS with aging is driven in part by the accumulation of body fat resulting from a positive energy balance. This “error” is sensed by the CNS via increases in adiposity-related humoral signals (e.g., leptin, insulin) that cross the blood-brain barrier, activate subcortical areas of the brain involved in the regulation of energy balance (e.g., ventromedial hypothalamus), and stimulate SNS outflow to peripheral tissues. The SNS activation is intended to increase  $\beta$ -adrenergic stimulation of thermogenesis in order to expend excess energy as heat rather than by additional storage of fat. However, the chronic sympathetic activation actually impairs  $\beta$ -adrenergic signaling and peripheral tissue responsiveness, further reducing  $\beta$ -adrenergic modulation of energy expenditure. Thus, the SNS activation initiated to prevent additional storage of body fat may with time evolve into a mechanism contributing to the development of obesity with aging. EEPA, energy expenditure due to physical activity.

#### TONIC SNS ACTIVATION WITH AGING IN ADULT HUMANS

Under supine resting conditions, plasma norepinephrine (PNE) concentrations increase  $\sim 10$ – $15\%$  per decade in adult humans (1,14), and total PNE spillover rates also are increased (15) (Fig. 2A), indicating a net increase in systemic (whole-body) SNS activity with advancing age (2). This increase in total SNS outflow to the periphery with human aging involves increases in SNS activity to the heart, skeletal muscle, and the liver/gut (3,6–8,16–18) (Fig. 2B–D). Renal PNE spillover is, on average,  $\sim 40\%$  higher in older compared with young men, although the differences do not attain statistical significance (6). In contrast, plasma epinephrine concentrations do not change with age, and epinephrine secretion from the adrenal medulla actually is reduced in older men (5). Thus, aging in adult humans is associated with a progressive and marked activation of the SNS to several peripheral tissues, with no significant change in circulating levels of epinephrine.

#### I. WHY DOES PERIPHERAL SNS ACTIVITY INCREASE WITH AGING IN HEALTHY ADULT HUMANS?

**Proposed stimulus for age-associated SNS activation: increases in adiposity.** We propose that a perceived “threat” to homeostasis that necessitates a CNS-mediated counterregulatory increase in SNS outflow to peripheral tissues with aging is a progressive elevation in body fat. This putative stimulus would seem to satisfy four key criteria:

**The stimulus must change progressively with adult aging.** Total body fat increases progressively with advancing age in the general population (19,20) (Fig. 3). This is not completely reflected by changes in body weight (mass), which increases to approximately the fifth decade and then plateaus and eventually declines at older ages as

a result of reductions in fat-free mass (19,20). The increase in adiposity with age is associated with reductions in total energy expenditure mediated by decreases in all three of its major components: resting metabolic rate (RMR), thermic effect of food (TEF), and physical activity–related energy expenditure (21,22) (Fig. 1). Total energy intake also declines with advancing age (23), but in general not quite as much as the decline in total energy expenditure. This produces a state of positive energy balance and storage of the excess energy as fat.

**The stimulus must be a regulated (defended) property.** It is well established that energy balance and fat storage are regulated functions, monitored and defended by the CNS (12,13,24). Excessive energy intake is associated with CNS-mediated increases in energy expenditure and complementary suppression of energy intake (appetite) aimed at restoring energy balance and preventing further fat storage (12,13,24–27). This compensatory response may have evolved during periods of poor nutrient food access to allow large amounts of energy to be consumed in order to meet nutritional needs without excessive storage of fat and weight gain. This system does not appear to be as physiologically robust as the response to underfeeding and a negative energy balance (12). The latter likely represented a much greater threat to survival during periods of food deprivation than did excess weight, which actually offered an evolutionary advantage (buffer) against starvation. Nevertheless, a positive energy balance appears to be a strong stimulus for SNS activation.

**The stimulus must require SNS activation as part of the counterregulatory response.** The classic studies of Landsberg and colleagues (25,26,28) first demonstrated in experimental animals that SNS activation to a variety of peripheral tissues is a key element of the CNS counterregulatory response to excessive energy intake. More recent studies have established that SNS activation is a

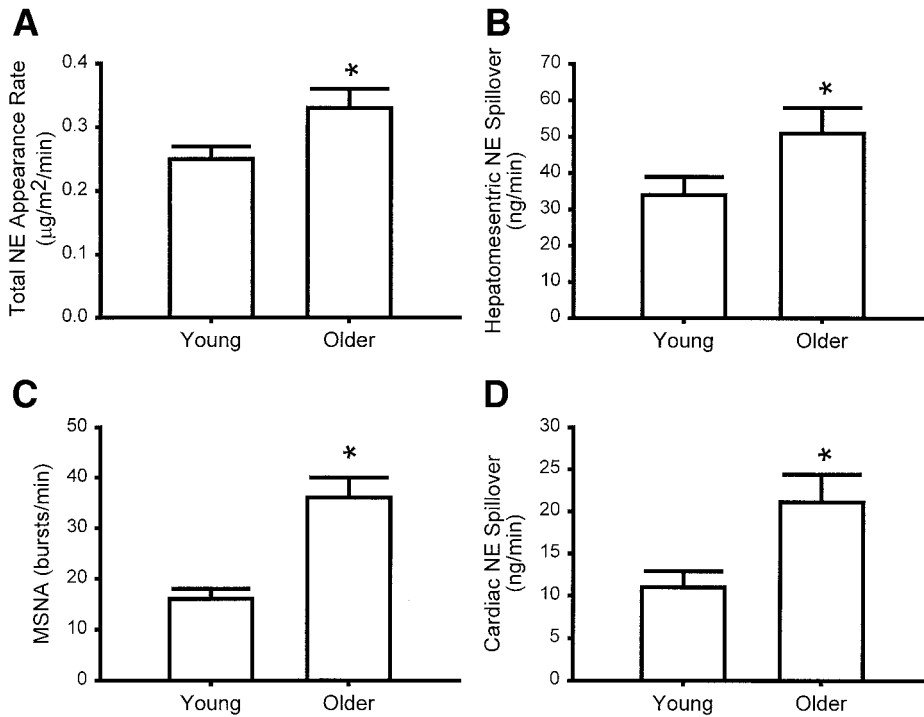


FIG. 2. Peripheral SNS activity is increased with aging in humans. A: Total norepinephrine (NE) appearance rate is greater ( $P < 0.05$ ) in older compared with young adults (15). SNS activity to the liver-gut (B) (18), skeletal muscle (C) (3), and heart (D) (6) is greater ( $*P < 0.05$ ) in older compared with young adults. Data are means  $\pm$  SE.

fundamental aspect of the integrative response to overfeeding in humans (29,30). The tonic SNS activation evoked by excess energy intake presumably is aimed at stimulating  $\beta$ -adrenergic thermogenesis to prevent further fat storage by expending the excess energy as heat (24). **The stimulus must be sensed by the CNS.** The exact mechanisms by which peripheral fat storage is controlled by the CNS are incompletely understood. However, there is extensive evidence that “adiposity signals,” such as circulating plasma concentrations of leptin and insulin, may inform the CNS as to the status of fat storage and help transduce an error message from the periphery into an appropriate efferent SNS response (12,28,31). These putative adipose-sensitive humoral signals would seem to meet the key requirements to act in such a regulatory manner. First, the plasma concentrations of leptin and insulin change in parallel with changes in fat storage (10–13). Second, leptin and insulin can cross the blood-brain barrier and access their respective receptors expressed in areas of the hypothalamus involved in CNS control of

energy intake and expenditure (12,13,31,32). Third, upon gaining access to these hypothalamic nuclei, leptin and insulin signaling results in excitation of SNS preganglionic neurons and an increase in postganglionic SNS activity to various tissues in the periphery (12,13,31–34).

**Evidence linking body fat storage to age-associated SNS activation in humans.** Total and abdominal fat stores increase with adult aging (19,20). Several lines of experimental evidence link one or both of these events with age-associated increases in whole-body SNS activity. For example, 24-h urinary norepinephrine excretion is positively related to BMI and both waist circumference and waist-to-hip ratio (measures of abdominal adiposity) among healthy adults aged 43–85 years (27). Moreover, percent total body fat and waist circumference correlate positively with age-associated elevations in total PNE appearance rates (35,36), explaining up to  $\sim 50\%$  of the interindividual variance in the latter (35). Consistent with these observations, reductions in waist circumference with caloric restriction are positively related to reductions

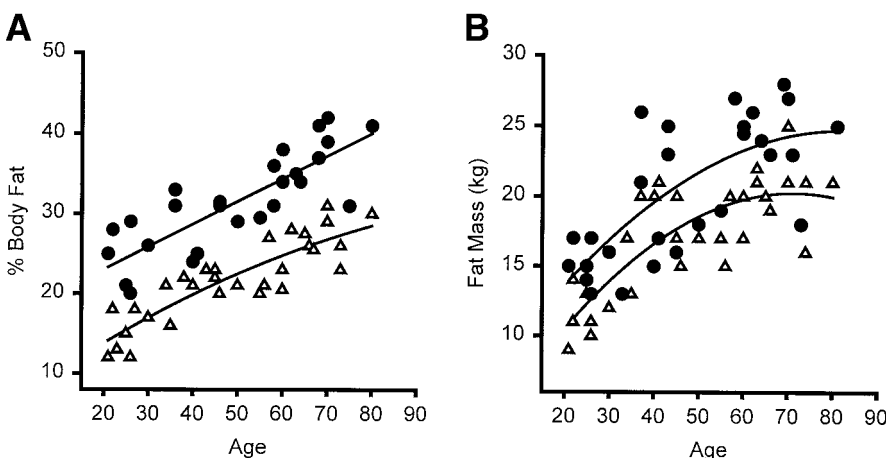


FIG. 3. Fat storage is increased with aging in humans. Open triangles represent males. Closed circles represent females. Figures adapted from ref. 19.

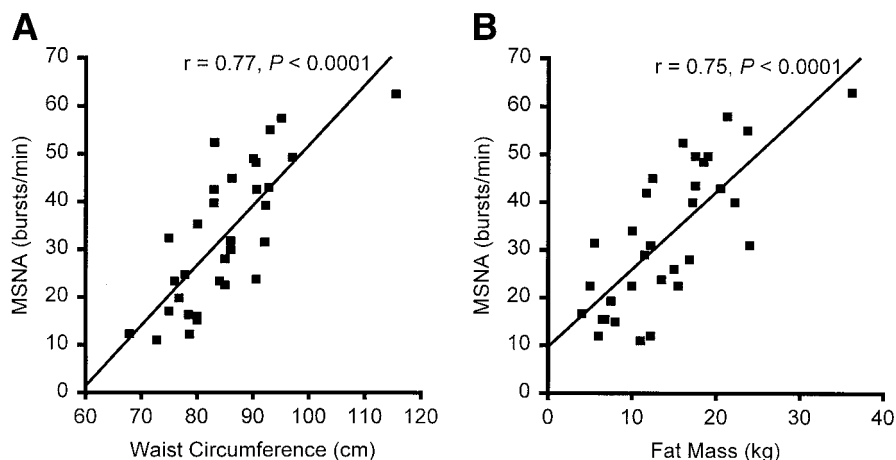


FIG. 4. Skeletal muscle appears to be one peripheral target of the adiposity-associated elevation in SNS outflow with aging. Skeletal MSNA is strongly and positively related to waist circumference and total fat mass in young and older males (8).

in total PNE appearance rates in middle-aged and older obese men (37).

Skeletal muscle appears to be one peripheral target of the adiposity-associated elevation in SNS outflow with aging. Among healthy young and older men, muscle sympathetic nerve activity (MSNA) is strongly and positively related to both percent body fat and waist circumference, with waist circumference alone explaining up to 60% of the interindividual variance in MSNA (8) (Fig. 4). MSNA also is positively related to percent body fat and waist circumference within cohorts of older men (9). In addition, the normal age-associated difference in MSNA is markedly reduced when young and older men of similar percent body fat and waist circumference are compared (9). Caloric restriction-induced weight loss results in significant reductions in MSNA in both young obese adults (38) and in middle-aged and older obese women (39). Recent findings in young adults suggest that abdominal visceral fat may be the strongest adiposity-associated correlate of MSNA in humans (40).

In summary, these observations collectively support a physiological coupling between age-associated increases in adiposity and peripheral SNS activity.

**Key connections: humoral signals and brain noradrenergic activity in adiposity-related peripheral SNS activation with aging in humans.** Our integrated working hypothesis would be strengthened by evidence linking the key afferent (increases in body fatness and adiposity signals), central (increased subcortical brain activation), and efferent (increased peripheral SNS activity) events in the proposed model.

**Adiposity-related increases in peripheral SNS activity with aging are associated with increased adiposity signals.** Plasma concentrations of insulin and leptin are strongly and positively related to body fatness in humans across the adult age range (10,11). However, only recently has evidence become available linking these putative adiposity signals with sympathoexcitation in humans. It is now clear that circulating levels of insulin and/or leptin, total and abdominal adiposity, and MSNA are all elevated in healthy older compared with young adults (10) (Fig. 5). Plasma insulin and leptin concentrations are positively related to MSNA among young adults and in healthy men varying widely in age (10,41) (Fig. 5). Indeed, plasma leptin concentrations are an independent predictor of MSNA among healthy young and older adult

males (10). Importantly, accounting for the influence of plasma leptin concentrations abolishes the significance of the relation between adiposity and MSNA in young and older men (10). Collectively, these observations provide support for the idea that body fat-associated elevations in peripheral SNS activity with aging in humans are positively related to circulating leptin concentrations and perhaps other putative adiposity signals. This postulated tonic stimulation of central SNS outflow by chronically elevated circulating leptin may occur as a consequence of “selective leptin resistance,” i.e., the concept that leptin’s sympathoexcitatory actions can be preserved in the face of resistance to its possible influence on appetite (42).

**Plasma leptin concentrations reflect CNS leptin concentrations.** If leptin is an adiposity signal stimulating

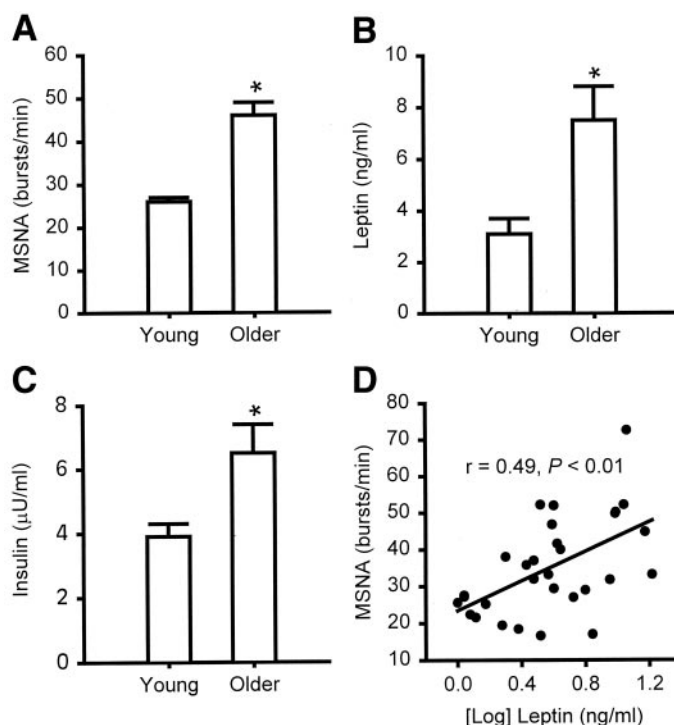


FIG. 5. Adiposity-related increases in peripheral SNS activity with aging are associated with increased adiposity signals. A, B, and C: Skeletal MSNA and plasma leptin and insulin concentrations are greater (\* $P < 0.05$ ) in older compared with young males (10). D: MSNA is positively related to plasma leptin concentrations in young and older healthy men (10). Data are means  $\pm$  SE.

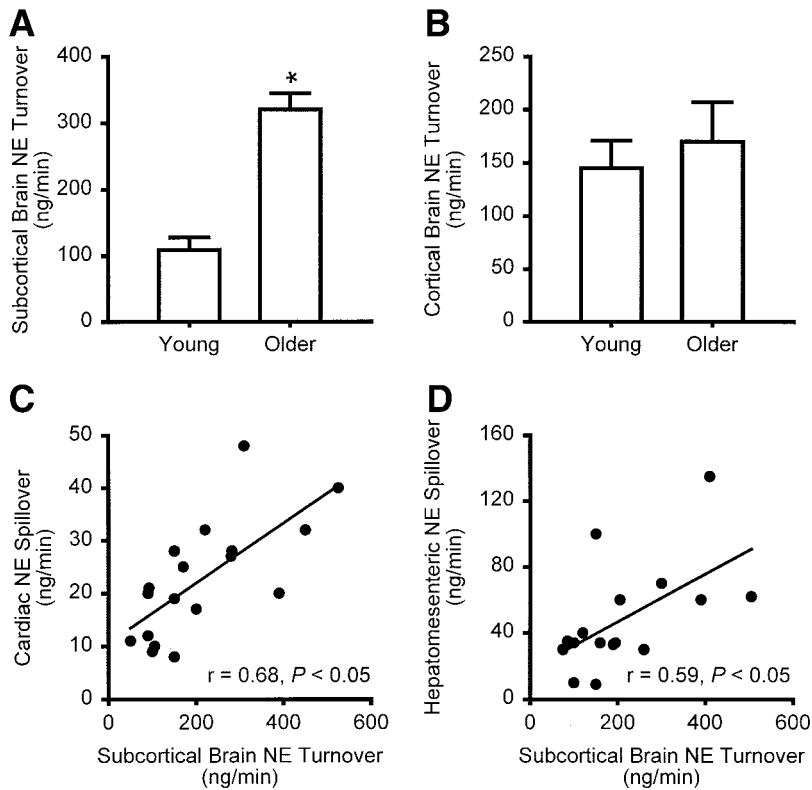


FIG. 6. Subcortical (A) but not cortical (B) brain noradrenergic activity is greater ( $*P < 0.01$ ) in older compared with young adults (49). Data are means  $\pm$  SE (C and D). Age-associated increases in peripheral SNS activity are positively related to supramedullary subcortical brain noradrenergic activity ( $0.59 < r < 0.68$ ,  $P < 0.05$ ) in young and older adults (49).

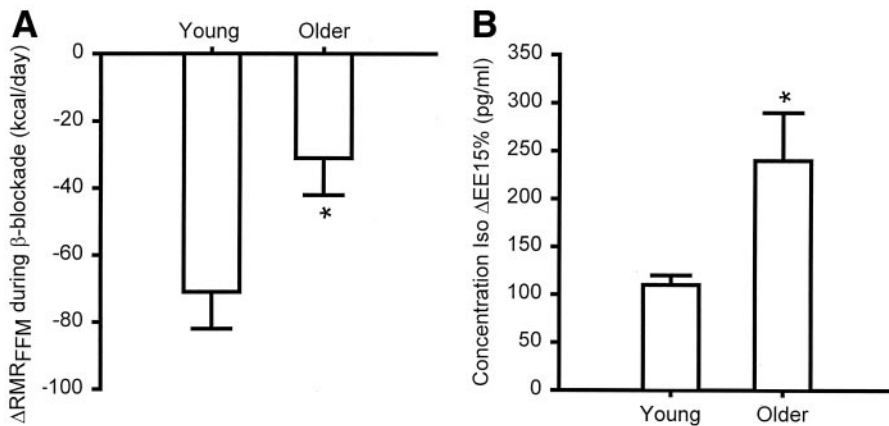
SNS outflow to the periphery with aging, it must act centrally to do so. Thus, whether peripheral concentrations of leptin reflect levels within the CNS of humans is an important element of the present hypothesis. In this regard, recently it has been established that peripheral plasma and cerebral spinal fluid concentrations of leptin are strongly and positively related in humans (43,44). These observations support the idea that the elevated plasma leptin concentrations with aging in adult humans reflect correspondingly elevated brain leptin concentrations. **Increased subcortical brain noradrenergic activity with aging.** If increased fat storage and centrally acting adiposity signals such as leptin are driving the tonically elevated peripheral SNS activity observed with adult aging, neuronal activity in areas of the brain involved in SNS control of energy balance should be stimulated. In this context, chemical destruction of noradrenergic nuclei in the ventromedial hypothalamus abolishes thermogenic SNS activity to brown adipose tissue and causes development of massive obesity in experimental animals (45). Subcortical supramedullary brain norepinephrine turnover has been used to examine the activity of noradrenergic neurons in areas of the brain known to control SNS outflow to peripheral tissues in intact conscious humans (17,46,47). Norepinephrine turnover in the cortical brain, an area not believed to influence SNS regulation, can be used as an internal control for the possibility of a nonspecific stimulation of brain noradrenergic neuronal activity.

Using this approach, subcortical brain norepinephrine turnover has been shown to be elevated in a number of conditions associated with chronic peripheral SNS activation, including in patients with essential hypertension and congestive heart failure (17,47,48). Recent findings demonstrate that subcortical supramedullary brain norepi-

nephrine turnover is approximately twofold greater, whereas cortical brain norepinephrine turnover is similar, in older compared with young healthy men (49) (Fig. 6A and B). Taken together, these observations are consistent with the idea of a selective increase in noradrenergic neuronal activity in subcortical supramedullary areas of the brain, including the hypothalamus, with primary human aging.

**Age-associated increases in peripheral SNS activity are related to increases in brain norepinephrine turnover.** The case for our working hypothesis would be advanced by evidence linking the marked increase in subcortical brain norepinephrine turnover with aging to corresponding increases in peripheral SNS activity. Recent findings support such a relation (49). Specifically, cardiac and hepatomesenteric norepinephrine spillover were increased in older compared with young healthy men, indicating augmented SNS outflow to the heart and liver/gut with aging. Most important, both of these increases in peripheral SNS activity were positively related to the age-associated increases in subcortical supramedullary brain norepinephrine turnover (Fig. 6C and D), whereas there were no correlations with cortical brain norepinephrine turnover. These results are consistent with the postulate that the peripheral SNS activation with adult aging in humans is linked to increases in subcortical brain noradrenergic activity.

**Regulatory goal of the age-associated increase in peripheral SNS activity with aging: increased  $\beta$ -adrenergic thermogenesis.** We propose that a key regulatory aim of the tonic increase in peripheral SNS activity with advancing age in humans is to increase  $\beta$ -adrenergic-mediated thermogenesis in order to prevent further fat storage. As discussed above, Landsberg (32) has demon-



**FIG. 7.**  $\beta$ -Adrenergic receptor sympathetic nervous system support of resting energy expenditure is smaller ( $*P < 0.05$ ) in older compared with young adults. This may be mediated by decreased  $\beta$ -adrenergic receptor responsiveness with aging. **A:** The decrease in RMR (adjusted for fat-free mass [FFM]) during systemic  $\beta$ -adrenergic receptor blockade is less ( $P < 0.05$ ) in older compared with young adults (11). **B:** The plasma concentration of isoproterenol, a nonspecific  $\beta$ -adrenergic receptor agonist, required to increase resting energy expenditure 15% above baseline is greater in older compared with young adults (55). Data are means  $\pm$  SE.

strated that sustained peripheral SNS activation is a fundamental physiological adjustment to increased fat storage in rats. Moreover, cross-sectional comparisons of obese and lean humans (50) and weight loss interventions in obese adults (38,39) support such adiposity-stimulated SNS activation in humans. Several lines of evidence from studies in both experimental animals and humans (29,51) have established that along with appetite suppression, CNS stimulation of metabolic rate is a basic physiological adjustment to an overfeeding-induced positive energy balance. Such increases in energy metabolism are mediated by the  $\beta$ -adrenergic signaling pathway in response to SNS activation in peripheral tissues (24). In humans, both  $\beta_1$  and  $\beta_2$  receptors contribute to the thermogenic response, whereas the role of  $\beta_3$  receptors has yet to be established (52). The fact that the tissues to which SNS activity is increased with aging, most prominently liver/gut and skeletal muscle, are among those believed to contribute the most to RMR (53) is consistent with an intention to stimulate thermogenesis. The key question, however, is if the peripheral SNS activation associated with human aging achieves this proposed regulatory goal of tonically augmenting  $\beta$ -adrenergic stimulation of metabolic rate.

## II. DOES THE SUSTAINED PERIPHERAL SNS ACTIVATION ASSOCIATED WITH HUMAN AGING ACHIEVE ITS INTENDED REGULATORY GOAL?

**Tonic  $\beta$ -adrenergic support of metabolic rate with aging.** If the tonic increase in peripheral SNS activity with aging achieves its immediate intended regulatory goal of stimulating  $\beta$ -adrenergic thermogenesis, then tonic  $\beta$ -adrenergic “support” of metabolic rate should be augmented in older compared with young adult humans.  $\beta$ -adrenergic support of resting energy metabolism has been established in young adults by demonstrating reductions in RMR with complete nonspecific  $\beta$ -adrenergic receptor blockade (intravenous propranolol) (54). Recent findings, however, indicate that the decrease in RMR with acute  $\beta$ -adrenergic receptor blockade is smaller, not greater, in healthy older compared with young sedentary adults (11); indeed, the older adults demonstrated no significant reduction in RMR from baseline in response to propranolol (Fig. 7A). These observations support the hypothesis that tonic  $\beta$ -adrenergic support of metabolic rate is reduced, not augmented, with adult aging in humans despite an age-associated increase in the stimulus (SNS activity).

**$\beta$ -Adrenergic tissue responsiveness to SNS stimulation with aging.** A reduction in  $\beta$ -adrenergic support of RMR with aging in the presence of elevated peripheral SNS activity suggests an age-associated decrease in  $\beta$ -adrenergic tissue responsiveness. This is consistent with the recent observation that significantly greater concentrations of isoproterenol, a nonspecific  $\beta$ -adrenergic receptor agonist, are required to produce a standardized increase in RMR in older compared with young healthy adults (55) (Fig. 7B). These results indicate that the primary mechanism underlying the tonic reduction in  $\beta$ -adrenergic support of RMR with human aging is a reduced tissue metabolic responsiveness to  $\beta$ -adrenergic receptor stimulation.

In addition to its impact on RMR, this reduction in  $\beta$ -adrenergic tissue responsiveness with aging may negatively affect other sources of energy expenditure in the older adult. Preliminary data from our laboratory suggests that the decrease in TEF with aging is associated with normal peripheral SNS activation in response to acute energy intake (oral glucose ingestion) (Fig. 8). Because 30–40% of TEF is mediated by the  $\beta$ -adrenergic pathway (56), these results are consistent with a role for reduced  $\beta$ -adrenergic responsiveness in the attenuated TEF observed in older adults.

Collectively, these findings support the idea that at least one of the key mechanisms underlying nonbody composition-related reductions in total energy expenditure with adult aging in humans involves decreases in RMR and TEF mediated by impaired peripheral metabolic responsiveness to  $\beta$ -adrenergic receptor stimulation. The latter is likely the result of desensitization of the  $\beta$ -adrenergic signaling pathway in response to chronic age-associated peripheral SNS activation (57). Together these events could presumably act to reduce the capacity for  $\beta$ -adrenergic thermogenesis in the older adult, rendering them more susceptible to fat storage of excess energy intake and future weight gain.

An interesting question is why the CNS, with its considerable “wisdom,” would adopt such an ultimately ineffective regulatory strategy? It’s not clear, but the most likely explanation is that the system simply doesn’t have a mechanism to sense these events. That is, there is no source of feedback to identify this “metabolic desensitization” of the  $\beta$ -adrenergic signaling pathway. Rather, the CNS continues to respond to what it perceives as an error in one or more of its key adiposity signals: body fat

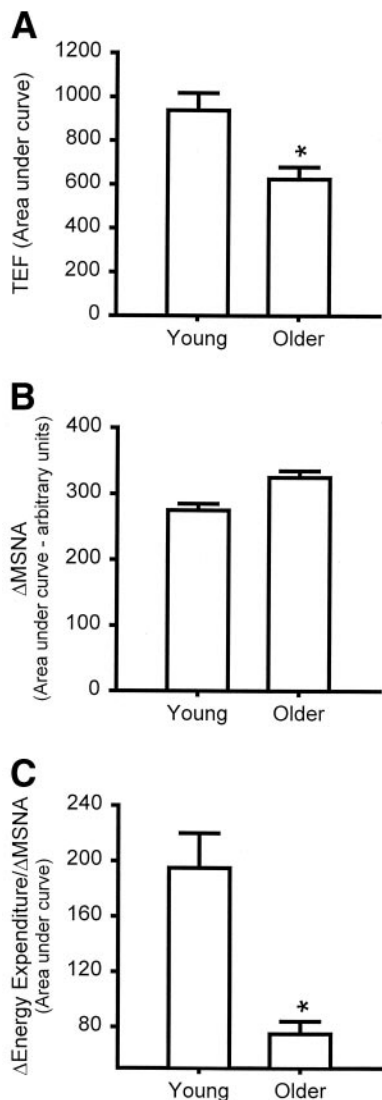


FIG. 8. The TEF is smaller ( $P < 0.05$ ) in older compared with young adults (A), despite similar postprandial increases in skeletal MSNA (B), resulting in a smaller ( $P < 0.05$ ) TEF per unit increase in MSNA (C). From P.P. Jones and D.R.S., unpublished data (mean  $\pm$  SE).

increases causing plasma insulin and/or leptin concentrations to increase, which increases the counterregulatory activation of the SNS, further desensitizing the  $\beta$ -adrenergic signaling pathway and reducing its stimulation of energy expenditure, facilitating additional storage of fat in an ongoing vicious cycle. A classic case of good regulatory intentions gone bad.

**Evidence linking impaired  $\beta$ -adrenergic stimulation of energy expenditure to future weight gain.** The potential physiological and clinical impact of these proposed events would be more compelling if there was evidence that tonic suppression of  $\beta$ -adrenergic stimulation of energy expenditure, as occurs with human aging, is directly linked to enhanced fat storage and weight gain. Currently, there is no direct support for this possibility from research on humans. However, recent findings demonstrating augmented body weight gain in transgenic mice without  $\beta$ -adrenergic receptors indicate an important role for  $\beta$ -adrenergic thermogenesis in determining the susceptibility for future weight gain (58). The greater increase in

body weight in these “ $\beta$ -less” mice was associated with similar food intake, but reduced metabolic rate compared with their wild-type controls, implicating the absence of  $\beta$ -adrenergic stimulation of energy expenditure (diet-induced thermogenesis) as the key mechanism involved. Importantly, when given access to a high-fat diet the  $\beta$ -less mice rapidly developed massive obesity. Taken together, these observations demonstrate an important role for  $\beta$ -adrenergic thermogenesis in stimulating metabolism and determining future body weight gain during intake of both normal and energy-dense diets in mice.

Indirect evidence supporting a role for the  $\beta$ -adrenergic signaling pathway in diet-induced thermogenesis and the control of body weight in humans can be derived from clinical trials involving  $\beta$ -receptor antagonists (59,60). Specifically, increased weight gain has been observed in some patients taking  $\beta$ -blockers compared with patients taking placebo (59–61). These observations are consistent with the idea that impaired  $\beta$ -adrenergic thermogenesis is associated with increased weight gain in adult humans.

**Potential impact of impaired  $\beta$ -adrenergic modulation of metabolic rate in age-associated obesity.** If our theory is to have merit physiologically, impaired  $\beta$ -adrenergic modulation of energy expenditure must be able to explain, at least in part, age-associated increases in adiposity and body weight gain. In general, SNS  $\beta$ -adrenergic stimulation of metabolism appears to account for somewhere between 3 and 5% of RMR (11,54), i.e.:

- 52–88 calories/day based on an average RMR of 1,750 calories/day in an ~25-year-old male
- 45–75 calories/day based on an average RMR of 1,500 calories/day in an ~65-year-old male.

Moreover, SNS  $\beta$ -adrenergic stimulation is believed to explain 30–40% of TEF (56), i.e.:

- 105–140 calories/day based on an average TEF of 350 calories/day in an ~25-year-old male
- 75–100 calories/day based on an average TEF of 250 calories/day in an ~65-year-old male.

If total energy expenditure of these representative young and older males was ~3,500 and 2,700 calories/day, respectively, the SNS  $\beta$ -adrenergic signaling pathway could be responsible for 228 and 175 calories/day (~6.5% of total daily energy expenditure). If viewed on a longer-term basis, this  $\beta$ -adrenergic contribution amounts to ~83,220 and 63,875 calories/year, respectively (of a total of ~1,200,000 and ~800,000 calories/year). Because adult weight gain with advancing age averages 1–2 lbs (~0.5–1 kg)/year (3,500–7,000 excess calories/year if thermogenically “uncompensated,” 7,000–14,000 excess calories/year with 50% thermogenic compensation), it is clear that even small reductions in  $\beta$ -adrenergic stimulation of metabolic rate could explain the increases in adiposity observed with aging in humans.

#### SUMMARY AND PERSPECTIVE

In the present treatise, we have advanced an integrated hypothesis that may help explain the etiology of the increase in peripheral SNS activity that occurs with pri-

mary aging in adult humans. In doing so, we also have assessed if this postulated cause for age-associated SNS activation achieves its presumed regulatory aim. We conclude that there is sufficient experimental evidence to suggest that at least a significant portion of the augmentation in peripheral SNS activity with human aging may be driven by the intention of the CNS to stimulate metabolic rate in order to prevent further storage of fat. If so, we also must conclude, however, that not only does this "adjustment" not achieve its goal of stimulating metabolism, but it may actually worsen the situation by leading to impaired  $\beta$ -adrenergic thermogenesis and reduced resistance to fat storage. As such, the chronic SNS activation associated with aging in humans may be considered both a consequence and a cause of obesity in middle-aged and older adults.

In an earlier article focusing on the development of obesity-related hypertension, Julius et al. (61) hypothesized that the SNS activation associated with hypertension may produce  $\beta$ -adrenergic desensitization and susceptibility to obesity. On the same topic of obesity hypertension, Landsberg recently speculated that "as subjects (patients with hypertension) age and the effectiveness of thermogenic mechanisms wanes, obesity might develop as a consequence of increased caloric intake no longer effectively buffered by the increased SNS activity" (31). We suggest here that a similar process may be occurring with human aging in the absence of clinical disease.

If true, the present hypothesis has important clinical implications for the aging adult. Given the consequences of age-associated increases in adiposity in producing  $\beta$ -adrenergic desensitization and reduced diet-induced thermogenesis, our observations point to the importance of minimizing the accumulation of body fat with aging. As adiposity increases, our vulnerability for further fat storage increases. These events also would suggest that lifestyle behaviors and/or drugs that maintain  $\beta$ -adrenergic responsiveness and thermogenesis with advancing age may be effective in combating the development of age-associated obesity.

Finally, we wish to emphasize that this discussion is presented as a working hypothesis. Although we have attempted to anchor as many of the key elements as possible with peer-reviewed scientific data, we recognize that, as with any working hypothesis, some important pieces of the puzzle are not yet in place. We also recognize the existence of results not necessarily consistent with the ideas submitted here. However, our primary purpose is to advance a new model, the crucial aspects of which can be tested experimentally in the future. Given the importance of age-associated increases in adiposity in the current obesity epidemic, it is more important than ever to submit testable concepts concerning the physiological mechanisms underlying this complex disorder in the hope of developing effective prevention and treatment strategies.

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