Animal aging and regulation of sympathetic nerve discharge

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Kenney MJ. Animal aging and regulation of sympathetic nerve discharge. J Appl Physiol 109: 951–958, 2010. First published July 22, 2010; doi:10.1152/japplphysiol.00506.2010.—Studies completed in human subjects have made seminal contributions to understanding the effects of age on sympathetic nervous system (SNS) regulation. Numerous experimental constraints limit the design of studies involving human subjects; therefore, completion of studies in animal models of aging would be expected to provide additional insight regarding mechanisms mediating age-related changes in sympathetic nerve discharge (SND) regulation. The present review assesses the current state of the literature regarding contributions from animal studies on the effects of advancing age on SND regulation, focusing primarily on studies that have used direct recordings of sympathetic nerve outflow. Few studies using direct SND recordings have been completed in animal models of aging, regardless of the fundamental component of SND regulation reviewed (basal levels, acute responsiveness, relationships between the discharges in sympathetic nerves, central neural regulation). SND responsiveness to various acute stressors is altered in aged compared with young animals; however, mechanisms remain virtually unexplored. There is a marked dearth of studies that have used central neural microinjection techniques in conjunction with SND recordings in aged animals, making it difficult to develop an evidence-based framework regarding potential age-associated effects on central regulation of SND. Determination of age-related changes in mechanisms regulating SND is important for understanding relationships between chronic disease development and changes in SNS function; however, this can only be achieved by substantially extending the current knowledge base regarding the effects of age on SND regulation in animal studies.

sympathetic nervous system; central nervous system; acute stress

The sympathetic nervous system (SNS) plays a critical role in the regulation of physiological homeostasis under basal conditions and in response to acute and chronic stressors. Central sympathetic neural circuits regulate numerous aspects of sympathetic nerve outflow, including the level of sympathetic nerve discharge (SND), the SND bursting pattern, and the relationships between discharges in nerves innervating diverse targets (2, 46–48, 88). SNS regulation in humans is altered with advancing age, including age-related changes in resting levels of muscle and skin sympathetic nerve activity, autonomic support of arterial blood pressure (ABP), and SND responses to acute stress (19–21, 28, 44, 45, 71, 82, 83).

Clinical and experimental studies have documented a number of pathophysiological states that are characterized by SNS dysregulation (4, 8, 17, 23, 27, 29, 38, 45, 60, 63, 66, 75, 82). The incidence of many chronic disease states increases with advancing age (83), and recent data from the American Heart Association indicates that the majority of adult male and female Americans between the ages of 60 and 79 yr suffer from cardiovascular-related diseases (76a). It is estimated that worldwide the number of aged persons will increase dramatically in the next half century (94). Therefore, understanding age-dependent alterations in mechanisms regulating SND is pertinent for understanding relationships between chronic disease development and age-associated changes in SNS function. As stated by E. L. Schneider in the journal Science (80): “If our nation is serious about averting the future exponential growth of health care costs for the elderly, we must start now by providing adequate funding for the prevention and effective treatment of the chronic diseases that afflict the older population.” Based on the demographics of the aging population and the role of SNS dysregulation in age-related diseases, it is imperative that the biomedical research community strive for a more thorough understanding of age-associated changes in SNS regulation.

The current review discusses key experimental observations associated with the effects of age on SND regulation in animal models. The physiology of SNS regulation and function involves many steps (e.g., centrally mediated sympathetic nerve outflow, neurotransmitter synthesis and release, neuronal reuptake of neurotransmitter, termination of neurotransmitter action, adrenergic receptor effects), several of which are influenced by advanced age (45, 82). This topical review focuses on the results of human and animal studies that have used direct SND recordings, as they provide a measure of central neural-generated sympathetic nerve outflow. The first section presents a brief overview of studies focused on age-related changes in SND regulation in human subjects, providing the conceptual
framework for discussing in a second section the effects of age on SND regulation in animals. Age-related changes in SNS regulation in humans are well investigated (19–21, 28, 44, 45, 71, 82, 83); however, the influence of age on SND regulation in animal models has not been recently reviewed. This is a significant omission, because validation of SNS changes in aged animals provides a parallel model for studying age-associated changes in SND regulation and lays the foundation for the design and completion of more mechanically driven studies than those that can be performed in human subjects.

**SND REGULATION AND HUMAN AGING: BRIEF OVERVIEW**

This section provides a brief overview of studies that have documented in human subjects the effects of age on regulation of basal SND, SND responsiveness to acute stress, and central neural regulation of SND.

**Age and Regulation of Basal SND**

As reviewed by Seals and Bell (82), aging in adult humans is associated with marked SNS activation directed to selective targets. Total norepinephrine (NE) spillover, hepatomesenteric NE spillover, muscle SND, and cardiac NE spillover are higher in older compared with young adults (71, 82). In contrast, skin SND is reduced in aged compared with middle-aged and young human subjects, and renal NE spillover has been reported to be similar in young and aged human subjects (22, 28). Epinephrine secretion from the adrenal medulla was reduced in aged compared with young men, demonstrating a functional consequence of age-related changes in the autonomic nervous system support of ABP in human subjects (44).

**Age and SND Responses to Acute Stress**

As reviewed by Seals and Esler (83), it has been thought for many years that aged humans demonstrate sympathetic hyperactivity to acute stress. However, this concept has been reconsidered based in part on studies using direct recordings of muscle SND (83). Ng et al. (72) and Davy et al. (14) reported that increases in the absolute level of muscle SND in response to various acute stressors were similar in young and aged subjects. Because resting levels of muscle SND were higher in the older subjects, relative increases in muscle SND to periods of acute stress tended to be reduced in aged compared with young subjects (14, 72). Monahan and Ray (69, 76) reported that aging attenuates muscle SND responses to activation of the vestibulospinal reflex. Similarly, Esler et al. (20) found that, in response to a variety of stressors, secretion of epinephrine from the adrenal medulla was reduced in aged compared with young men. These findings support the view that human aging is likely not associated with heightened sympathoadrenal activation to acute stress, at least with respect to muscle SND and, in fact, suggest that sympathetic responsiveness to selected stimuli may be reduced with advancing age.

**Age and Central Neural Regulation of SND**

Central neural mechanisms mediating age-associated changes in SND regulation remain largely unknown. In one study designed to determine possible age-related changes in central neural regulation of the SNS in human subjects, Esler and colleagues (19) measured central nervous system NE turnover under basal conditions in young and aged men. These investigators reported increased suprabulbar subcortical turnover of NE, along with enhanced NE spillover in the heart and hepatomesenteric circulations, in aged compared with young subjects (19), suggesting a possible role for altered central catecholamine regulation in age-associated SND changes in human subjects.

In a recent review, Monahan (68) stated that there is little convincing evidence demonstrating age-related alterations in sympathetic baroreflex sensitivity with regards to regulation of muscle SND in human subjects. Subsequently, Studinger et al. (87) provided new insight regarding the effect of age on the relationship between SND and baroreflex function. These investigators reported that aged subjects demonstrated reduced sympathetic activation to decreases in ABP due to stiffening of barosensory vessels, but a more sensitive inhibition of SND in response to increases in ABP due to enhanced regulation of SND (87). It was suggested that the enhanced control of SND may be mediated by age-associated changes in central neural circuits, although mechanisms remain unknown (87). In summary, a paucity of information exists concerning the effects of age on the physiology of central sympathetic neural circuits in human subjects.

**ANIMAL AGING AND SND REGULATION**

This section reviews studies that have documented in animal subjects the effects of age on regulation of basal SND, SND responsiveness to acute stress, and central neural regulation of SND.

**Age and Regulation of Basal SND**

Sympathetic nerves innervating the heart, blood vessels, and visceral organs are tonically active, and the background level of SND in anesthetized young (3- to 5-mo-old), middle-aged (12-mo-old), and aged (24- to 25-mo-old) Fischer 344 (F344) rats is characterized by the presence of synchronized bursts (49). Similarly, muscle SND in young and aged human subjects is characterized by the presence of synchronized discharge bursts (72, 83). As demonstrated using power density spectral analysis, the basal SND bursting pattern contains a prominent cardiac-related component in baroreceptor-innervated young, middle-aged, and aged rats (49). These data suggest that, in rodents, there are no obvious age-associated changes in the basal SND bursting pattern, the signature output of sympathetic neural circuits.

The interpretation of the absolute level of efferent SND and the comparison of SND levels between groups in animal preparations is problematic. The level of activity in multifiber SND recordings is influenced by a number of factors, including the proximity of the recording electrodes to sympathetic nerve fibers, the number of active nerve fibers, recording conditions, and the use of bipolar recording techniques. Based on these methodological considerations, the level of SND is typically reported as percent change.
from control for each animal, making it difficult to determine whether aging affects basal SND. Despite these limitations, several studies have compared the absolute level of SND in animals at different ages. Hajduczok et al. (31) reported that renal SND was nearly 10-fold higher in aged (11-yr-old) compared with young (1-yr-old) anesthetized beagles when carotid sinus pressure was held at 50 mmHg. In contrast, baseline levels of renal SND have been reported to be similar in conscious aged (24-mo-old) compared with young (10-wk-old) Wistar rats (39) and in conscious mature (12-mo-old) compared with aged (24-mo-old) F344 rats (84). The observations suggesting that basal levels of renal SND are similar in rats of different ages are consistent with data from human studies indicating that renal NE spillover does not differ in young and aged human subjects (20, 21). However, not only is there little information regarding the effect of age on basal renal SND, there is virtually no information available in animals regarding the effect of age on basal levels of activity in nerves innervating targets other than the kidney. This is a significant omission, because an important organizational strategy employed by the SNS to regulate resting physiological functions involves selective regulation of efferent SND (70).

Advancing age in animals affects baroreflex regulation of basal SND. Reflex inhibition of splanchnic SND is attenuated in anesthetized middle-aged (9-mo-old) compared with young (2-mo-old) Sprague-Dawley rats (92), and baroreflex regulation of renal SND is impaired in conscious aged (24-mo-old) compared with young (10-wk-old) Wistar rats (39) and in aged compared with young anesthetized beagles (30, 31). It has been speculated that altered central regulation contributes to the attenuated reflex reduction of renal SND in aged beagles (30, 31). On the other hand, baroreflex-mediated inhibition of adrenal SND has been reported to be similar in anesthetized young and aged Wistar rats (58). One possibility that should be considered is that age-related changes in baroreflex regulation of SND may be nerve specific.

In summary, it appears that advancing age in rodents does not alter the fundamental characteristics of the basal SND bursting pattern. Several factors must be considered, however, before specific conclusions can be drawn regarding the effect of age on basal levels of SND in animals. Because of inherent difficulties in comparing SND levels between different age groups in animal preparations, and because the level of activity in a single nerve innervating a specific target cannot be generalized to the regulation of activity in nerves innervating other targets, the use of direct SND recordings in animals for determining possible age-related effects on basal levels of SND remains problematic. This may be an area of sympathetic neurophysiology, where the most definitive data, at least as it relates to muscle SND, are derived from studies involving human subjects. Future studies should consider the use of ganglionic blockade experiments to determine whether autonomic regulation of ABP differs in aged compared with young animals.

Age and SND Responses to Acute Stress

SND responses to acute stress depend on the specific experimental stimulus and the peripheral nerve from which activity is being recorded. The effect of age on SND responses to various experimental stressors is reviewed below.

Hyperthermia. Acute heating increases muscle SND in young, conscious humans (11, 74), splanchnic SND in young, conscious rats (57), and SND directed toward visceral organs in young, anesthetized rats (47, 50, 52). In addition, the pattern of SND bursts is altered during elevations in body temperature (47). Specifically, the cardiac-related SND bursting pattern is transformed during heating to a pattern that contains low-frequency, noncardiac-related bursts in young, anesthetized rats (47). Hyperthermia-induced, low-frequency SND bursts contain more activity than cardiac-related bursts, establishing SND pattern transformation as an important strategy for mediating sympathoexcitation to heat stress in young rats (47).

Aging alters cardiovascular responses to heat stress in human subjects (67). Minson et al. (67) found that increases in cardiac output to heating were attenuated in older (70 ± 3 yr) compared with young (23 ± 1 yr) men due to a significant fall in stroke volume in the aged subjects, and also reported there was less redistribution of blood flow from the splanchnic and renal circulations during heating in older compared with young men. Consistent with these data, Kenney and Fels (49) reported that renal and splanchnic sympathoexcitatory responses to heating were significantly attenuated in aged (24-mo-old) compared with young (3-mo-old) anesthetized F344 rats. Age-related differences in SND responses to progressive hyperthermia were evident in both baroreceptor-intact and baroreceptor-denervated rats (49). In addition, the SND bursting pattern was changed during heating in young but not in aged rats (49). Stauss et al. (84) reported that the level of renal SND remained unchanged in response to hyperthermia in 12- and 24-mo-old conscious F344 rats. One factor that may contribute to the attenuated SND responses to hyperthermia in aged rats may be that the basal level of activity in these animals is at the physiological maximum. This is unlikely, as application of a short bout of combined hypoxia and hypercapnia, a stimulus that produces intense sympathoexcitation in young rats, increases SND from levels recorded at peak hyperthermia in aged rats (49). Kenney and Musch (51) reported a marked attenuation in heating-induced vascular conductance changes in aged (24-mo-old) compared with young (3-mo-old) rats, suggesting a functional consequence for the altered SND responses to heating with advanced age.

Hypothermia. Cold stress influences SND regulation, and nonuniform changes in SND are produced by spinal cord cooling in decerebrate rabbits (40) and via whole body hypothermia in young rats (48). Visceral sympathoinhibitory (adrenal, renal, splenic) responses to acute cooling are more heterogeneous and not as robust in middle-aged (12-mo-old) and aged (24-mo-old) compared with young (3- to 6-mo-old) anesthetized F344 rats (33), suggesting that advancing age exerts a significant modulatory influence on SND responses to hypothermia.

Hypoxia. The effects of age on adrenal SND responses to differing levels of acute inspired hypoxia in anesthetized rats have been studied by Sato and colleagues (78, 79). Compared with normoxia (end-tidal O₂ ~18%), hypoxia (end-tidal O₂ reduced to 10%) increased adrenal SND in aged (24- to 26-mo-old) but not in young (4- to 5-mo-old) rats, whereas adrenal SND responses to end-tidal O₂ concentrations of 8 and 6% did not differ between age groups (78). In contrast, adrenal sympathoexcitatory responses to severe hypoxia (end-tidal O₂, 3 and 2%) were significantly attenuated in aged compared with
young rats (79). In response to moderate hypoxemia in conscious rats, Kregel (56) reported that ABP remained unchanged in mature (12-mo-old) F344 rats, but was reduced by 24 mmHg in aged (24-mo-old) F344 rats, indicating age-related alterations in the ability to maintain ABP in response to this challenge. Although SND recordings were not completed in this latter study, in response to hypoxia, kidney and liver NE turnover rates were reduced in aged compared with mature F344 rats (56). The results of these studies suggest that advancing age influences sympathetic nerve regulation to systemic hypoxia.

Air-jet stress. Air-jet stress is an acute experimental intervention that influences SND regulation in young animals (15, 16, 55, 61, 62). Although age-related differences in physiological responses were modest, Stauss et al. (85) reported attenuated increases in ABP and low-frequency blood pressure power (an indirect indication of SND) and shorter duration elevations in renal resistance and renal SND to air-jet stress in aged (24-mo-old) compared with mature (12-mo-old) conscious F344 rats. These data suggest that advancing age may attenuate SND responsivity to application of this psychological/environmental stressor.

Cutaneous stimulation. The effects of age on SND responses to stimulation of cutaneous afferents has been determined in several studies (58, 90). Cardiac SND responses to pinching of the hindpaw and chest skin are similar in anesthetized young (4- to 7-mo-old), aged (24- to 27-mo-old), and very old (32- to 36-mo-old) Wistar rats (90). Moreover, adrenal SND responses to pinching and brushing of the chest skin are similar in anesthetized young (4-mo-old) and aged (26-mo-old) Wistar rats (58). These results suggest that aging does not prominently affect cardiac and adrenal SND responses to nociceptive and nonnoceceptive cutaneous stimulation.

Glucose administration. Adrenal SND responses to glucose administration (73) do not appear to be age dependent, as Sato et al. (78) reported similar levels of adrenal sympathoinhibition to intravenous glucose administration in anesthetized young (4- to 5-mo-old) and aged (24- to 26-mo-old) Wistar rats.

In summary, the available data from studies involving directly recorded SND indicate that animal aging is associated with altered SND regulation in response to selected experimental stimuli. The results of several studies support the concept that the responsiveness of sympathetic neural circuits to specific stimuli is attenuated in aged compared with young or mature rats. As reviewed by Cizza et al. (7), the capacity of mammals to maintain homeostasis in response to acute stress declines with advancing age, an effect that may be related to age-associated declines in sympathetic neural responsivity. However, several factors must be considered before specific conclusions can be drawn regarding the effect of age on SND responsiveness to acute stress in animals. First, the current literature search revealed a small number of studies that have compared directly recorded SND between rats at different ages in response to acute experimental interventions. Second, because age-associated sympathetic alterations in humans involve regional selectivity (45, 83), it is imperative that the discharges in multiple sympathetic nerves be recorded during experimental interventions. However, for the most part, published studies have not compared SND responses to multiple targets between rats of different ages. Third, direct nerve recordings provide an experimental means to study multiple indexes of SND (e.g., level of activity, bursting pattern, relationships between the discharges in different sympathetic nerves), thereby providing a comprehensive profile of SND regulation. However, most studies involving experimental animals and SND responses to acute stress have not utilized detailed analyses of SND. Fourth, the majority of studies that have evaluated the effects of age on SND regulation have compared SND responses between rats at two selected chronological ages (e.g., young vs. aged; middle-aged vs. aged). There has not been a consistent emphasis to provide SND data in animals at multiple chronological ages (e.g., young, middle-aged, aged, very old). Fifth, recent studies have suggested that “biological age” rather than, or in addition to, chronological age may be a useful experimental measure for identifying the effects of age on physiological function (5, 9, 25, 64, 65). Biological markers of aging in rodents are suggested to include rapid and substantial loss of body weight, as well as changes in cold-induced thermoregulation, food intake, and circadian regulation of body temperature (5, 9, 25, 64, 65). To provide a more complete understanding of the effects of aging on SND regulation, consideration should be given to both chronological and biological markers of age.

Age and Central Regulation of SND

Forebrain, brain stem, and spinal neural circuits are involved in SND regulation in young and mature mammals (12, 13, 59, 86, 88, 89), suggesting complex interactions between multiple levels of the central neuraxis. Much of the contemporary understanding of central neural regulation of SND in young mammals has been determined using microinjection techniques and by functionally identifying neurons that are components of sympathetic neural networks using electrophysiological techniques. For example, studies using selective central sympathetic nuclei microinjections to activate excitatory amino acid receptors, antagonize GABA receptors, antagonize excitatory amino acid receptors, inhibit nitric oxide synthase, and inactivate neurons via muscimol or lidocaine have substantially shaped the current understanding of neurotransmitters, neuromodulators, and excitatory and inhibitory interactions involved in regulating SND in young animals (12, 13, 59, 86, 88, 89).

Altered regulation of central sympathetic neural circuits may be an important contributing factor to age-associated changes in SND regulation. Kaye and Esler (45) recently stated that methods used to study central regulation of human sympathetic outflow “do not have the topographic precision to allow study of specific nuclei or their projections.” In this regard, the determination of central mechanisms mediating altered SND regulation with aging likely requires the completion of studies in animal models of aging; however, little information is available. With this in mind, the following sections consider four possibilities.

Nucleus tractus solitarii, SND regulation, and aging. It has been hypothesized that impairments in central neural integration of baroreceptor afferent nerve activity may contribute to age-associated changes in SND regulation (30, 31). The nucleus tractus solitarii (NTS) is a brain stem area that plays a key role in SND regulation because this nucleus receives the majority of primary nerve endings of baroreceptor, chemoreceptor, and cardiopulmonary afferent fibers in the aortic depressor, carotid sinus, and vagus nerves (2, 13, 88). The NTS projects to numerous regions in the spinal cord, brain stem, and forebrain that are involved in SND regulation (2, 13, 88).

A role for age-related changes in NTS regulation of SND has been considered. Itoh and Bunag (42) reported that reductions
in ABP, heart rate, and renal SND to NTS serotonin microinjections were significantly attenuated in aged (24-mo-old) compared with young (2-mo-old) rats. These same investigators reported differences in baroreflex regulation of renal SND in young (3-mo-old) compared with mature (14-mo-old) rats following bilateral NTS 6-hydroxydopamine microinjections, suggesting that age-associated changes in baroreflex regulation may involve NTS catecholaminergic mechanisms (43). These results suggest that age-related changes in NTS physiology may contribute to altered regulation of SND, although this possibility has not been tested in a systematic or thorough manner. Although SND was not recorded, Arnold and colleagues (1) recently identified mechanisms in NTS regulation of heart rate in older (16- to 22-mo-old) transgenic rats with low glial angiotensinogen that involve endogenous angiotensins.

Forebrain nuclei, SND regulation, and aging. A recent study by Esler and colleagues (19) suggested the possibility for age-associated alterations in forebrain regulation of SND in humans. Are there corollary findings in animal models of aging? Both anatomical and functional data support a role for the hypothalamus in regulation of SND in young and mature animals (12, 13, 59, 86, 88), and several age-related changes in hypothalamic regulation of SND and ABP have been reported. For example, Tanabe and Bunag (93) reported lower stimulus thresholds and higher ABP and splanchic SND responses to electrical stimulation of the posterior hypothalamus in 10-mo-old compared with 2-mo-old rats. Similarly, Bezrukov et al. (3) reported reduced stimulus thresholds for eliciting increases in ABP (SND was not recorded) to electrical stimulation of anterior and posterior hypothalamic areas in aged compared with mature rats and rabbits. Although the interpretation of these data is limited due to the use of electrical stimulation techniques to activate hypothalamic areas, there is a suggestion that advanced age may enhance the responsiveness of hypothalamic neural circuits. However, little if any information is available comparing SND responses in young and aged animals to chemical activation/ina ctivation of selected hypothalamic or other forebrain nuclei. This is a significant omission, because hypothalamic neural circuits make important contributions to SND regulation in young mammals. For example, it is well-established that the paraventricular nucleus of the hypothalamus (PVN) contributes to SND regulation (53), an effect that is prominently influenced by a tonic inhibitory tone mediated by GABA. In addition, PVN excitatory amino acids provide a tonic excitatory tone to PVN sympathetic neural circuits (53). The potential effect of age-related changes in hypothalamic or other forebrain nuclei on SND regulation remains understudied.

Rostral ventral lateral medulla, SND regulation, and aging. The rostral ventral lateral medulla (RVLM) is a brain stem region that plays a critical role in basal and reflex regulation of SND in young animals (12, 13, 59, 86, 88, 89). Bilateral inactivation of RVLM neurons by microinjections of muscimol or lidocaine produces marked reductions in SND (6, 24, 34, 81), and, under basal conditions, the level of activity of RVLM neurons is determined by a balance of excitatory and inhibitory inputs (12, 13, 35, 41, 54, 77). Few, if any, studies have been completed to determine SND responses to activation or inhibition of RVLM neural circuits in aged animals under basal conditions, or in response to specific interventions. As discussed previously, the results of recent studies by Kenney and Fels (49, 50) demonstrate attenuated SND activation to heating in aged rats. Hosking et al. (36) demonstrated that the profound activation of SND at peak hyperthermia in young rats is dependent on the integrity of RVLM neural circuits. However, mechanisms contributing to age-related alterations in SND regulation to acute heat stress remain unexplored. One hypothesis is that aging may shift the balance of RVLM regulation during heating to a state characterized by enhanced synaptic inhibition and reduced synaptic excitation.

Aging, neuronal loss, and SND regulation. Age-related changes in brain morphology and/or neuronal number may influence SND regulation. As reviewed by Dickstein et al. (18), multiple age-associated morphological alterations are evident in cortical neural circuits; however, whether similar changes occur in central sympathetic neural circuits has not been determined in a systematic or thorough manner. The effect of age on total neuronal number in selected central nuclei has been determined in several studies involving both human and animal subjects (9, 26, 37, 91); however, the effects of age on the number of identified neurons contained in sympathetic neural circuits remains largely unknown.

In summary, a dearth of information exists regarding the effects of age on central mechanisms regulating SND under basal conditions and in response to acute stress. These are significant omissions, because understanding how central sympathetic circuits change during normal aging is essential before the boundary between normal and pathological conditions can be understood.

CONCLUSIONS

The completion of eloquent studies in human subjects, using direct recordings of muscle SND and organ-selective NE kinetic analyses, have substantially shaped the contemporary understanding of the effect of age on SND regulation. However, numerous inherent constraints limit the design of experimental studies involving human subjects, supporting the idea that additional understanding of mechanisms mediating age-related changes in SND regulation are likely to be gleaned through animal studies. The present review assessed the contributions from studies using animals for determining the effects of advancing age on SND regulation.

Several points are summarized (Fig. 1). First, a role for age-related changes in central regulation of SND has been considered, although not in a systematic or thorough manner. In fact, so few studies have used central neural microinjection or anatomical techniques in conjunction with SND recordings in aged animals that it is difficult to develop an evidence-based framework regarding potential age-associated effects on central regulation SND. Importantly, determination of age-dependent alterations in central neural mechanisms regulating SND is required for understanding relationships between chronic disease development and age-associated changes in SNS function. Second, the results of several investigations demonstrate that SND responsiveness to acute stress is substantially altered in aged compared with young rats; however, mechanisms mediating these changes remain virtually unknown. Third, few studies have examined SND responses to multiple targets in rats at different ages, despite the fact that nonuniform regulation of sympathetic nerve outflow is an important organizational strategy employed by the SNS. Fourth, regard-
less of which fundamental component of SND is considered, (e.g., level of activity, bursting pattern, acute responsiveness, relationships between the discharges in sympathetic nerves), it is evident that few studies have used direct recordings of SND in animal models of aging. Fifth, studies have not consistently completed SND recordings in animals at multiple chronological ages (e.g., young, middle-aged, aged, very old). Sixth, few if any studies have considered the effects of both chronological and biological markers of age on SND regulation. Without question, a striking dearth of information exists regarding SND regulation in animal models of aging.

Several lines of investigation should be pursued to help fill the substantial gaps of knowledge that exist regarding SND regulation in animal models of aging. First, discrete microinjections of selected neurotransmitters, neuromodulators, and receptor agonists and antagonists would provide insight regarding the effects of age on the responsiveness of sympathetic neural circuits. Second, determining age-related alterations in the genomic and proteomic profile of selected neurotransmitter receptor systems, the regulation of specific neurotransmitters and neuromodulators, and the binding kinetics of specific receptor subunits would help establish mechanisms mediating age-associated changes in the responsiveness of sympathetic neural circuits. Third, the central regulation of SND involves multiple levels of the neuraxis; therefore, it is likely that numerous spinal cord, brain stem, and forebrain areas will need to be studied to determine age-related changes in central sympathetic neurophysiology. Fourth, the implementation of long-term sympathetic nerve recordings in conscious animals at multiple chronological and biological ages would substantially enhance the biomedical significance of experimental studies. Fifth, most aging studies that involve SND recordings have used animals that are not afflicted by chronic pathophysiological conditions (e.g., heart failure, hypertension), despite knowing that the incidence of many chronic disease states increases with advancing age (83). For example, after an extensive review of the published literature, it appears that most, if not all, studies (>40) aimed at determining heart failure-induced alterations in sympathetic nerve outflow using direct SND recordings in rats have used young heart failure rats as the model of choice, despite the fact that the majority of heart failure patients are aged (29).

A recent textbook written by Dr. Louis Cozolino, entitled The Healthy Aging Brain (10), examines the aging brain from a perspective of interpersonal neurobiology. The author states, “with neuroscience discoveries shedding light on how our life courses play out, we need a new, more balanced story of aging to guide us into the decades ahead.” The structural and functional brain changes described in this text include cortical, hippocampal, and cerebellar changes. There is no mention of age-related changes in forebrain and brain stem sympathetic neural circuits, and for good reason, because these vital areas of the brain remain virtually unexplored with respect to aging. As stated by Dr. Cozolino (10), a “more balanced story of aging” is required; however, this can only be achieved by extending our current knowledge through new investigations.
knowledge base regarding aging and central neural regulation of SNS function.

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