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REVIEW ARTICLE

Brainstem noradrenergic neurons: Identifying a hub at the intersection of cognition, motility, and skeletal muscle regulation

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Abstract

Brainstem noradrenergic neuron clusters form a node integrating efferents projecting to distinct areas such as those regulating cognition and skeletal muscle structure and function, and receive dissimilar afferents through established circuits to coordinate organismal responses to internal and environmental challenges. Genetic lineage tracing shows the remarkable heterogeneity of brainstem noradrenergic neurons, which may explain their varied functions. They project to the locus coeruleus, the primary source of noradrenaline in the brain, which supports learning and cognition. They also project to pre-ganglionic neurons, which lie within the spinal cord and form synapses onto post-ganglionic neurons. The synapse between descending brainstem noradrenergic neurons and pre-ganglionic spinal neurons, and these in turn with post-ganglionic noradrenergic neurons located at the paravertebral sympathetic ganglia, support an anatomical hierarchy that regulates skeletal muscle innervation, neuromuscular transmission, and muscle trophism. Whether any noradrenergic neuron subpopulation is more susceptible to damaged protein deposit and death with ageing and neurodegeneration is a relevant question that answer will help us to detect neurodegeneration at an early stage, establish prognosis, and anticipate disease progression. Loss of muscle mass and strength with ageing, termed *sarcopenia*, may predict impaired cognition with ageing and neurodegeneration and establish an early time to start interventions aimed at reducing central noradrenergic neurons hyperactivity. Complex multidisciplinary approaches, including genetic tracing, specific circuit labelling, optogenetics and chemogenetics, electrophysiology, and single-cell transcriptomics and proteomics, are required to test this hypothesis pre-clinical.

KEYWORDS

ageing, cognition, motility, noradrenergic neurons, skeletal muscle

1 | INTRODUCTION

1.1 | The central autonomic nervous system

Extensive interconnections between the autonomic nervous system, endocrine, somatic, and limbic circuitry, provide the basis for behavioural arousal, emotion, stress responses, homeostasis, pain modulation, blood pressure and respiratory control, and micturition, and defecation reflexes.[1,2] This system consists of three anatomically distinct divisions: sympathetic, parasympathetic, and enteric,[3] and receives modulatory input from cholinergic, monoaminergic, and peptidergic neurons, as well as signals mediated by nitric oxide, purines, endocannabinoids, and neurosteroids.[4] Visceral inputs regulate autonomic output through both the sympathetic and parasympathetic pre-ganglionic neurons in the medulla, spinal cord, and the forebrain arousal system.[5]

The central autonomic nervous system includes monoaminergic neurons in the brainstem reticular formation and nuclei[6] that use monoamines such as serotonin, histamine, or the catecholamines dopamine, adrenaline, and noradrenaline (NA) as neurotransmitters.[7]

Most monoaminergic and acetylcholinergic neurons form cephalo-caudal longitudinally oriented clusters rather than compact groups of cell bodies. The first clusters were identified as the "A" cell groups and correspond to either noradrenergic (A1–A7) (Figure 1) or dopaminergic (A8–A14) neurons in rodents.[1] Noradrenergic neurons control many autonomic functions,[8,9] including cognition, stress response, selective attention, and memory,[2] and their organization and location are similar to those reported in humans.[10]

The serotoninergic system finds the primary location in two main raphe nuclei. These nuclei include nine neuronal subgroups (B1–B9)[11] that constitute the major pathways involved in affective responses and reward signals.[12–14] The superior raphe group, localized in the mesencephalon and the rostral pons, innervates the midbrain and forebrain, while the inferior raphe group, localized in the medulla and caudal pons, innervates the cerebellum, pons, medulla, and spinal cord.[11]

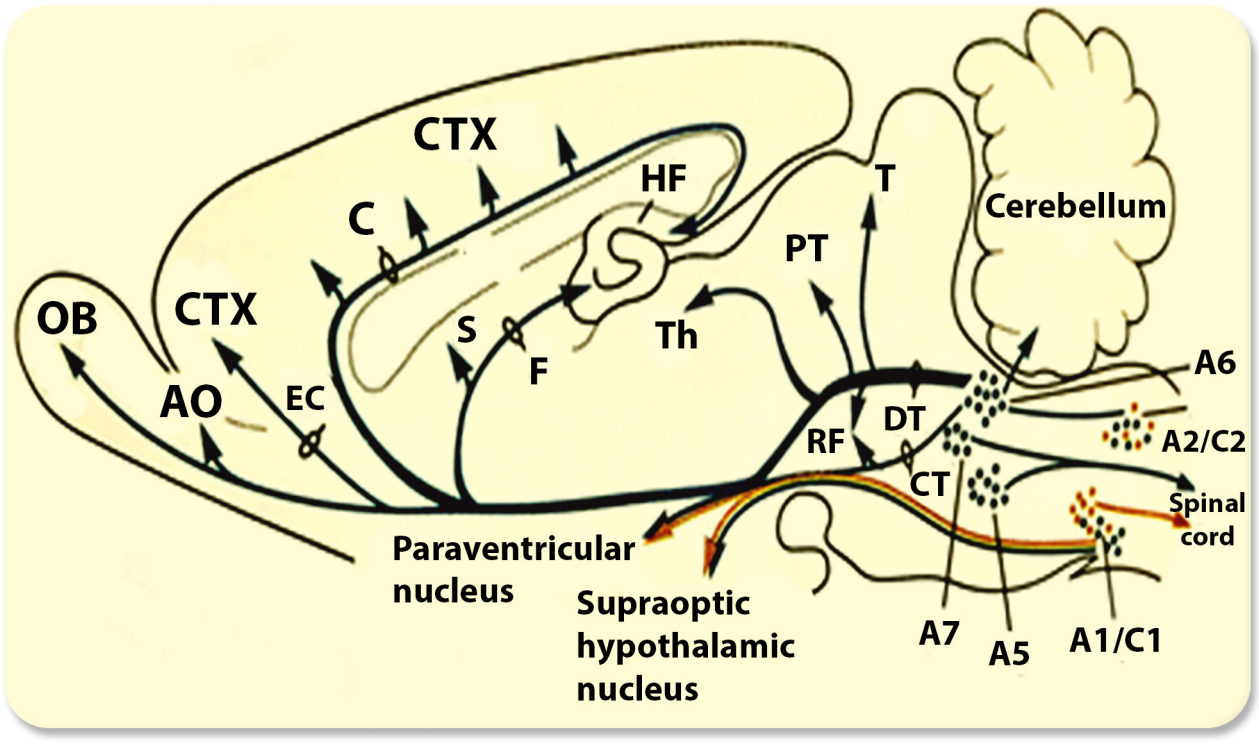

FIGURE 1 Brainstem noradrenergic and adrenergic neurons. Scheme of rat medulla and pons noradrenergic (A groups) and adrenergic (C groups) neurons. The A2 and C2, located in the dorsal medulla, are part of the nucleus of the solitary tract. A1 and C1 and located near the nucleus ambiguous. The location of A neuron groups is similar to that described in the human brainstem.[10] Arrows indicate noradrenergic neuron projections. Darker lines and dots correspond to noradrenergic neurons, while brown lines and dots to adrenergic neurons. AO, anterior olfactory nucleus; C, cingulate bundle; CC, corpus callosum; CT, central tegmental tract; CTX, cerebral cortex; DT, dorsal tegmental bundle; EC, external capsule; F, fornix; HF, hippocampal formation. OB, olfactory bulb; PT, pretectal nuclei; RF, reticular formation; S, septum; T, tectum; Th, thalamus. Adapted from Ref. [1]

C1–C3 neurons process other catecholamines to generate adrenaline. Particularly, C1 neurons form a rostral extension from the A1 column in the rostroventral medulla and project to the sympathetic pre-ganglionic column, where they provide tonic excitatory input to vasomotor neurons, regulate sympathetic response to haemorrhage, mediate a stress-induced anti-inflammatory reflex, and activate sympathetic and breathing outputs, among other functions.[15–17]

All histaminergic neurons, mainly located in the posterior lateral hypothalamus, form five minor associated clusters (E1–E5), considered the control center for wakefulness.[18]

Cholinergic neurons (Ch1–Ch6) are found in the pons and midbrain and non-brainstem areas, such as the thalamus and pre-ganglionic neurons located in the spinal cord intermediolateral column.[1,19] They regulate wake/sleep cycles[20,21] and, together with noradrenergic neurons, provide the final peripheral sympathetic pathway for regulation of neuromuscular transmission and skeletal muscle innervation.[22–28]

This review focuses on the potential involvement of brainstem noradrenergic neurons in cognition and skeletal muscle composition and function.

2 | BRAINSTEM NORADRENERGIC NEURONS EXHIBIT COMPLEX INTERCONNECTIONS AND PROJECTIONS

Brainstem noradrenergic neuron clusters form a complex system. They project to local segmental (brainstem), cephalic (telencephalon and diencephalon), and caudal (spinal cord anterior, lateral, and dorsal horns) regions of the central nervous system. Together with the parasympathetic nervous system, this noradrenergic neuron network accounts for the integrated organismal response to physiological or pathological challenges.[1] Increased sympathetic activity is associated with better cognitive performance in individuals over 65 years,[29] leading researchers to posit interactions between the autonomic nervous system and higher-level brain functions in neurological and neuropsychiatric disorders.[30] Furthermore, autonomic activity during sleep predicts memory consolidation in humans.[31] Although the role of the autonomic nervous system, particularly noradrenergic neurons, in higher brain function in health and disease has been studied for some time,[32–35] research on its involvement in controlling neuromuscular transmission, skeletal muscle innervation and mass, and motility, is more recent.[22–28]

Three noradrenergic neuron clusters—A5, A6, and A7—show extensive descending projections to the spinal cord. The A5 group projects segmentally to A6, with a possible role in cognition, and spinally, to target pre-ganglionic cholinergic neurons in the intermediolateral column (IML). The synapse between A5 pre-ganglionic and post-ganglionic noradrenergic neurons located at the paravertebral sympathetic ganglia support a role in skeletal muscle regulation. Skeletal muscle post-ganglionic sympathetic neuron projections have been related to neuromuscular organization, transmission, and skeletal muscle mass maintenance with development and ageing.[22–26]

The A6 cluster, or *locus coeruleus* (LC), projects to the globus pallidum, cerebellum, midbrain, amygdala, and various hypothalamic areas. It is the primary source of NA in the brain, supporting learning, and cognition.[36,37] It also projects to the dorsal horn of the spinal cord to regulate pain perception[38–40] and plays a role in sensory-motor behaviour.[41–43]

A7 neuron terminals are closely related to the cholinergic motoneurons in the ventral horn and may influence motor output through NA binding to noradrenergic receptors expressed by the ventral horn neurons.[44–46]

3 | ORIGIN AND DETERMINATION OF NORADRENERGIC NEURON SUBPOPULATIONS

A5 neurons are located ventrolaterally at the pons next to the inferior olive and medial to the facial nerve; the cluster extends between plates 74 and 81 of the Paxinos mouse stereotaxic atlas.[47] A5 and other adult brainstem norepinephrinergic neurons originate in the neural crest; their genetic lineage is distinct, and their heterogeneity becomes more pronounced during migration.[48,49] Bone morphogenetic proteins (BMPs) induce transcription factors Phox2b and Mash1 to activate the NA biosynthesis enzymes tyrosine hydroxylase (TH) and dopamine-beta-hydroxylase (DBH). Phox2b and Mash1 also induce expression of the Phox2a, dHand, and Gata3 transcription factors. Their role in NA biosynthesis and maintenance of the differentiated properties of TH and DBH neurons has been established (Figure 2).[26,50,51] Some crest cells adopt glial fates under the influence of neuregulin-1.[52]

In rodents, transcription factors Phox2b, Hand2, and Gata3 induce noradrenergic neuron differentiation on day 10 of embryonic development, while Phox2b and Hand2 evoke neurogenesis on day 13 and noradrenergic differentiation on days 14–15. Gata3 is required for neuronal survival on day 11 and peri-natal days,[51] while Hand2 is

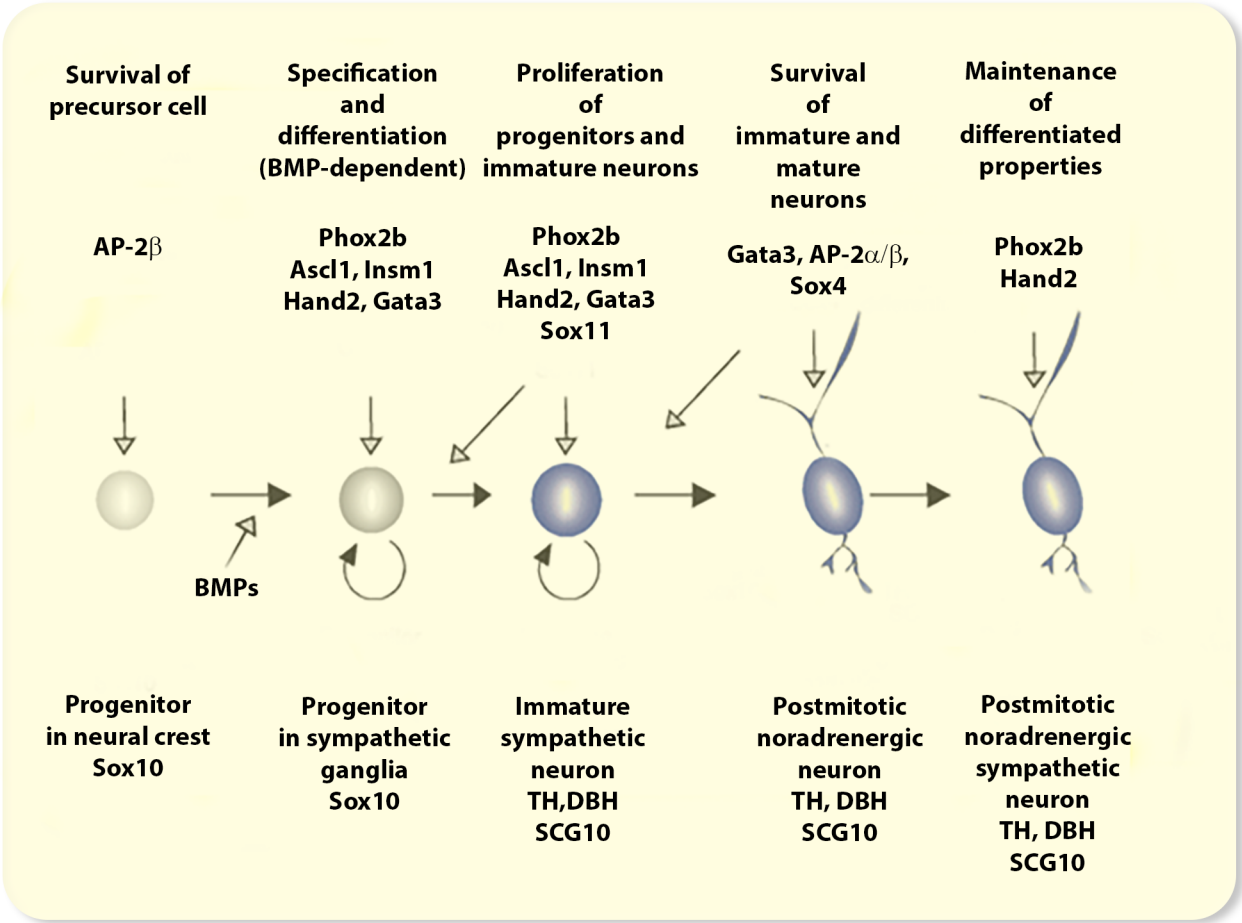

FIGURE 2 A set of transcription factors determines sympathetic neuron development and maintenance. (A) Gene regulatory network controlling sympathetic neuron specification, differentiation, proliferation, survival, and maintenance. (B) Target-derived signals regulate the resulting functional subtype of sympathetic neurons as illustrated for cholinergic differentiation of sudomotor neurons, mediated by the gp130 cytokine-induced Satb2 transcriptional regulator. BMP, bone morphogenetic protein; ChAT, choline acetyltransferase; DBH, dopamine-beta-hydroxylase; TH, tyrosine hydroxylase; VAChT, vesicular acetylcholine transporter. Adapted from Ref. [51]

necessary for ganglionic neuron maintenance during ageing and senescence.[22,24]

In humans, immunoreactivity to TH detected immature cell bodies in the brainstem at 4 weeks of gestation, followed by structural differentiation during the first trimester. Immunoreactive neuron prolongations began to appear at 5 weeks in the cervical spinal cord.[53] The location of A1–A2 and A5–A7 neuron groups agree with Dahlstroem and Fuxe's classification at 5–6 weeks gestational age.[54]

In addition to A5, the other anatomically defined nuclei of the adult brainstem include the LC, dorsal subcoeruleus (SubCD), and ventral subcoeruleus (SubCV) formations and A7, C2/A2, and C1/A1 neural groups.[47] Whether defining A5 neurons according to their genetic lineage will reveal the kind of projections (ascending, segmental, or descending) they extend to specific neuron targets and their contribution to functionality is unknown.[48] The neural tube in the hindbrain region, which gives rise to the rhombencephalon, is segmented into various rhombomeres (r), defined by their expression of transcription factors, such as *En1* (r1), *Hoxa2* (r2), *Krox20* (r3), *Hoxb1* (r4), and *Krox20* (r5), and presumptive derived noradrenergic neurons (r6-8) (Figure 3).[48]

Rhombomere r1-derived NA neurons populate the LC, SubCD, and A7 nuclei, but not the A5 neuron group; r2-derive neurons are consistently found in the LC, SubCD, SubCV, A7, and A5 nuclei; r3 and r5-derived neurons populate the SubCV and A5 pontine clusters as well as a small fraction of the C2/A2 and C1/A1 medullary group; r4-derived neurons contribute the most NA neurons to the SubCV and A5 pontine cluster.[48]

Thus, A5 has a complex neuronal composition derived from four rhombomeres: *Hoxa2* (r2), *Krox20*- (r3 and r5), and/or *Hoxb1* (r4). Its neuron projections to the central autonomic nervous system, including regions of the amygdala, hypothalamus, bed nucleus of the stria terminalis, insular cortex, and the cerebellum

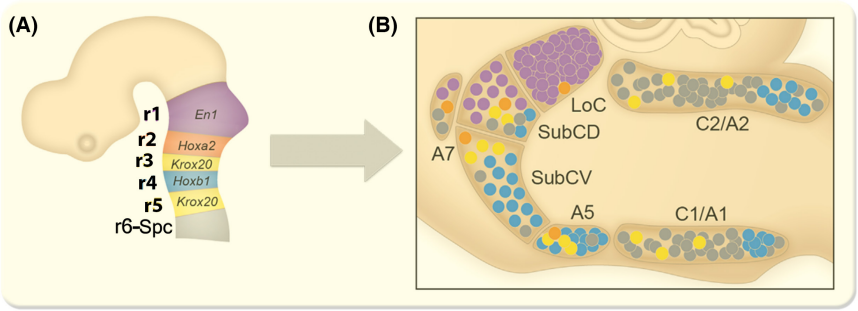

FIGURE 3 Identification of brainstem noradrenaline neurons defined by genetic lineage tracking using intersectional genetic fate mapping. (A) Sagittal view of the embryonic mouse brain showing rhombomere 1–8 of the hindbrain. (B) Adult mouse sagittal section, showing anatomically defined nuclei of the transcription factors *Hoxa2* (r2), *Krox20*- (r3 and r5), and/or *Hoxb1* (r4); genes provide the signature of the heterogenous A5 neuronal group. LoC, locus coeruleus; SubCD, subcoeruleus dorsal; subCV, subcoeruleus ventral. Adapted from Ref. [149]

in addition to the somatosensory cortex, the hindbrain, the parabrachial nucleus, and the LC, reflect its complex anatomical and functional organization. Identified genetically and/or by retrogradely labelled procedures,[48,55] its projections may play a role in processing threatening stimuli,[56] body homeostasis, autonomic and neuroendocrine functions,[57] cognition,[58] and balance and posture.[59]

Genetic tools that discern gene expression history and differences in rhombomeric origin allow us to identify the early developmental events that contribute to mature NA neuron subtypes. In contrast to LC, which consists predominantly of *En1*-derived cells,[48] the A5 neuronal group is populated by three rhombomere-derived subpopulations plus a fourth of unidentified origin.[48] Thus, heterogeneity is a primary factor confounding the interpretation of A5 and other brainstem noradrenergic neuron physiology throughout life.

4 | BRAINSTEM NORADRENERGIC NEURONS PROJECTION TO LC AND SPINAL CORD

To define the projection circuits and targets of a specific neuronal subpopulation, retrograde transsynaptic labelling with viral or non-viral vectors is a necessary complement to the intersectional genetic-fate mapping approach. Fluorescent viral vectors allow researchers to identify brainstem NA neuron projections to the adrenal medulla, sympathetic ganglia, cranial ganglia, and enteric neurons.[48] Retrograde transport of injected horseradish peroxidase-wheat germ agglutinin (HRP-WGA) then defined A5 projections to the sixth or seventh level of the thoracic spinal cord (IML).[55] Adeno-associated viral vector encoding GFP under an artificial DBH (PRSx8) promoter defined A5, LC, and A7 neurons' spinal projections. With some overlap, these three pontine neuronal clusters project predominantly to the IML, dorsal horn, and ventral horn, respectively, indicating that the LC may have the greatest effect on somatosensory transmission; the A7 group on motor function; and A5 on sympathetic function.[40] The A5 area shows up to 93% of noradrenergic neurons, a finding confirmed by preventing HRP migration in rats injected with 6-hydroxydopamine at the midthoracic spinal cord level. The high percentage of A5 noradrenergic neurons is consistent with previous and more recent reports.[38,60–62]

Recordings in anaesthetized and paralyzed rats showed that A5 neuron conduction velocity is 2.5 m/s and with a discharge rate of up to 4 spikes/s, which were inhibited by the α2-adrenergic agonist clonidine or desmethylimipramine.[63] Later, injecting a retrograde adeno-associated virus vector targeting EGFP or mRFP expression to sympathetic neurons (Figure 4) showed that pontine noradrenergic neurons project to the lower lumbar segments (L4 and L5) of the spinal cord.[38] This study also showed the circuits interconnecting A5 and A6 neurons by injecting a viral vector directly to the second group and analyzing its anterograde and retrograde tracing and expression.[38] Thus, brainstem noradrenergic neuron clusters integrate memory and higher brain functions, sensory perception, visceral function regulation, and, potentially, neuromuscular junction (NMJ) transmission and skeletal muscle trophism.

5 | THE INFLUENCE OF CENTRAL NORADRENERGIC NEURONS ON SYMPATHETIC AND MOTOR SKELETAL MUSCLE INNERVATION AND MOTILITY

The NMJ is a specialized synapse, anatomically modelled as a tripartite structure consisting of an alpha motoneuron

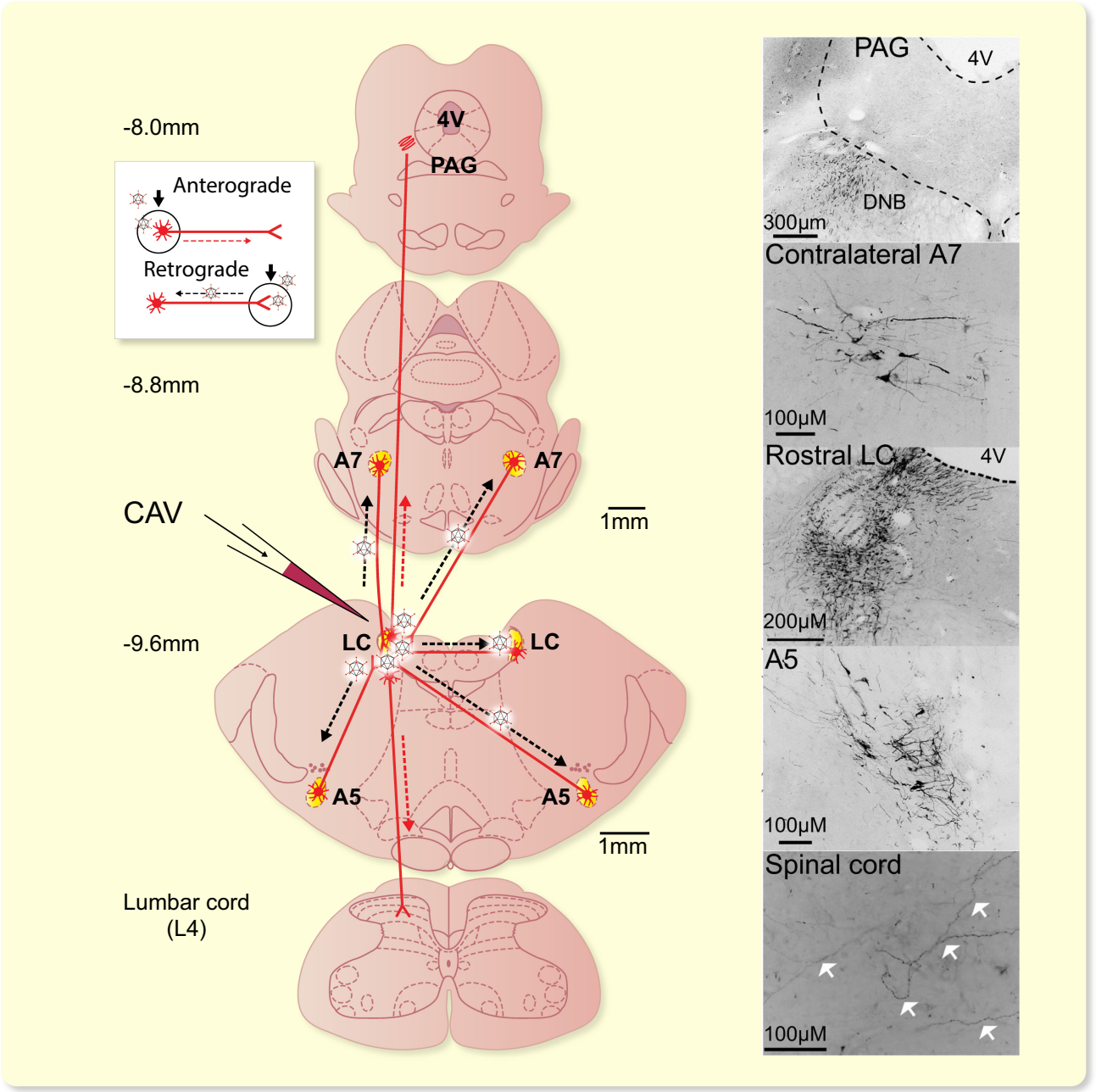

FIGURE 4 Segmental LC and A5 neurons connection. Diagram. After direct injection into the LC, the E1/E3-deleted, replication-defective, CAV-2 vector harboring the PRS promoter CAV2-PRS-ChR2-mCherry transduces LC noradrenergic neurons locally and retrogradely in the contralateral LC and in the A7 and A5 cell groups both ipsilateral and contralaterally. LC axons also show ascending projections to the midbrain (dorsal noradrenergic bundle, DNB) and descending to the spinal cord lumbar L4 level. Histological sections show mCherry fluorescence converted to grey-scale at DNB, contralateral A7, rostral LC, A5, and spinal cord. 4 V, fourth ventricle; PAG, peri-aqueductal grey. Adapted from Ref. [150]

terminal, a myofiber post-terminal, and peri-synaptic Schwann cells.[64] The NMJ plays a critical role in sustaining muscle mass, strength, posture, and locomotion throughout life.[65–69] Defining the mechanisms by which the sympathetic nervous system regulates these neuromuscular properties may also have broad health implications, particularly on gait and mobility in older adults.

Activation of peripheral sympathetic neurons increases NMJ transmission through a well-defined noradrenergic regulation of motoneuron adrenergic receptors.[22,45] However, the specific central nervous system neurons that account for the influence of post-ganglionic neurons on NMJ transmission remain unknown. Are the post-ganglionic sympathetic neurons regulated by central

autonomic relays, including spinal cord pre-ganglionic and brainstem noradrenergic neurons?

Previous studies have associated the LC with human mobility, motility, and skeletal muscle physiology.[70–75] A series of experiments in our laboratory focused on lumbar post-ganglionic sympathetic neurons and the LC, a subdivision of which projects to pre-ganglionic neurons in the spinal cord IML column. Combining optogenetics, a technique that uses laser pulses to control the activity of neurons that have been genetically modified to express light-sensitive ion channels, with electrophysiological recordings of NMJ transmission, provided a unique opportunity to determine the precise role of post-ganglionic sympathetic neurons and LC neurons in NMJ transmission in adult mice.[24] We crossed Ai32(RCL-ChR2[H134R/EYFP])[76] and TH-Cre mice[77] to create a model that expresses channelrodhopsin-2 (ChR2) in the central and peripheral noradrenergic neurons. We concluded that ganglionic sympathetic axons, but not LC optostimulation, enhanced NMJ transmission in vitro and in living mice by activating the β1-adrenergic receptor. We stimulated LC at frequencies below and above 5 Hz with no obvious response, which indicates that by innervating the muscle spindle,[78] LC modulates posture,[79] but not NMJ transmission. Based on the dense projections of A5 to pre-ganglionic spinal cord neurons and their subsequent projections to post-ganglionic neurons, future experiments should establish whether and how they modulate the motoneuron-dependent control of muscle innervation and NMJ transmission.

Detailed analysis of central neuroanatomical circuitries shows that, in addition to A5, several brainstem noradrenergic regions project to the IML, including the noradrenergic bulbospinal A1 and A2 areas[80] and pontine A6 and A7.[40] Elucidating the functional relevance of these central nervous system projections for NMJ transmission and muscle motor innervation would help in defining the coordinated response of the visceral and neuromuscular system to internal and environmental challenges in health and disease.

Electrical stimulation of various midbrain, pons, and rostral medulla sites in freely moving rats elicited a variety of motor responses, which were attributed to the activation of descending spinal or ascending brain projections.[73] The heterogeneity of brainstem noradrenergic neurons may account for their differential effects on various targets. We propose that the subgroup of A5 neurons that projects to the spinal cord IML may regulate muscle structure and function, while the group that projects to the LC, and through it to the anterior cingulate cortex and the basolateral amygdala areas may add another layer of control to sensory perception and memory consolidation.[81–83] Forty percent of A5 neurons projected to the thoracic spinal cord have a visceral vasomotor sympathoexcitatory function as determined by antidromic activation and clonidine-mediated neuron inhibition approaches.[84,85] Pseudorabies virus injections in the rat medial gastrocnemius muscle label A5 neurons among other brainstem noradrenergic clusters[86]; however, whether A5 neurons play a role in muscle structure and function remains to be experimentally examined.

Since post-ganglionic sympathetic neurons regulate skeletal muscle motoneuron innervation, neuromuscular transmission, and muscle mass and strength with ageing,[22–25,87] the position of A5 neurons at the top of the anatomical hierarchy, suggests they contribute to skeletal muscle physiology through their projection to the spinal cord IML (Figure 5). Since A5 neurons also project to the LC, the main NA source to the amygdala, these neurons may also regulate memory and cognition. The two A5 neuron subgroups can be identified by retrograde markers whose expression is driven by a dopamine-beta-hydroxylase promoter injected at the IML or LC. Such studies may show whether spinally projected A5 neurons are more susceptible to phosphor-tau deposition than those that project to the LC and explain why motor deficits precede cognitive impairment in Alzheimer's disease (AD).[88,89] A similar dichotomy has been examined to understand analgesia and aversion/anxiety functions, respectively, under the control of spinal- or prefrontal-projecting LC noradrenergic neurons.[90] Electrode arrays could be used to record the function of brainstem neuron clusters in awake rodents[91,92] but not at the cellular level, which demands combining complex approaches, including genetic tracing, specific circuit labelling, opto/chemogenetics, electrophysiology, and single-cell transcriptomics and proteomics.

6 | PRE-GANGLIONIC NEURONS INTEGRATE CENTRAL DESCENDING SYMPATHETIC INFORMATION, AND THEIR OUTPUT CONVERGES ONTO POST-GANGLIONIC SYMPATHETIC NEURONS

Pre-ganglionic neurons play a crucial role in the communication between the central and peripheral autonomic nervous systems because complex central segmental and suprasegmental inputs converge onto them.[93] These neurons lie within the spinal cord and their axons traverse the ventral horn to exit through ventral roots where they form synapses with post-ganglionic neurons. Pre-ganglionic neurons exhibit a rostrocaudal organization that ensures segmental patterning connectivity with specific cell targets.[94] Most pre-ganglionic neurons are unmyelinated,

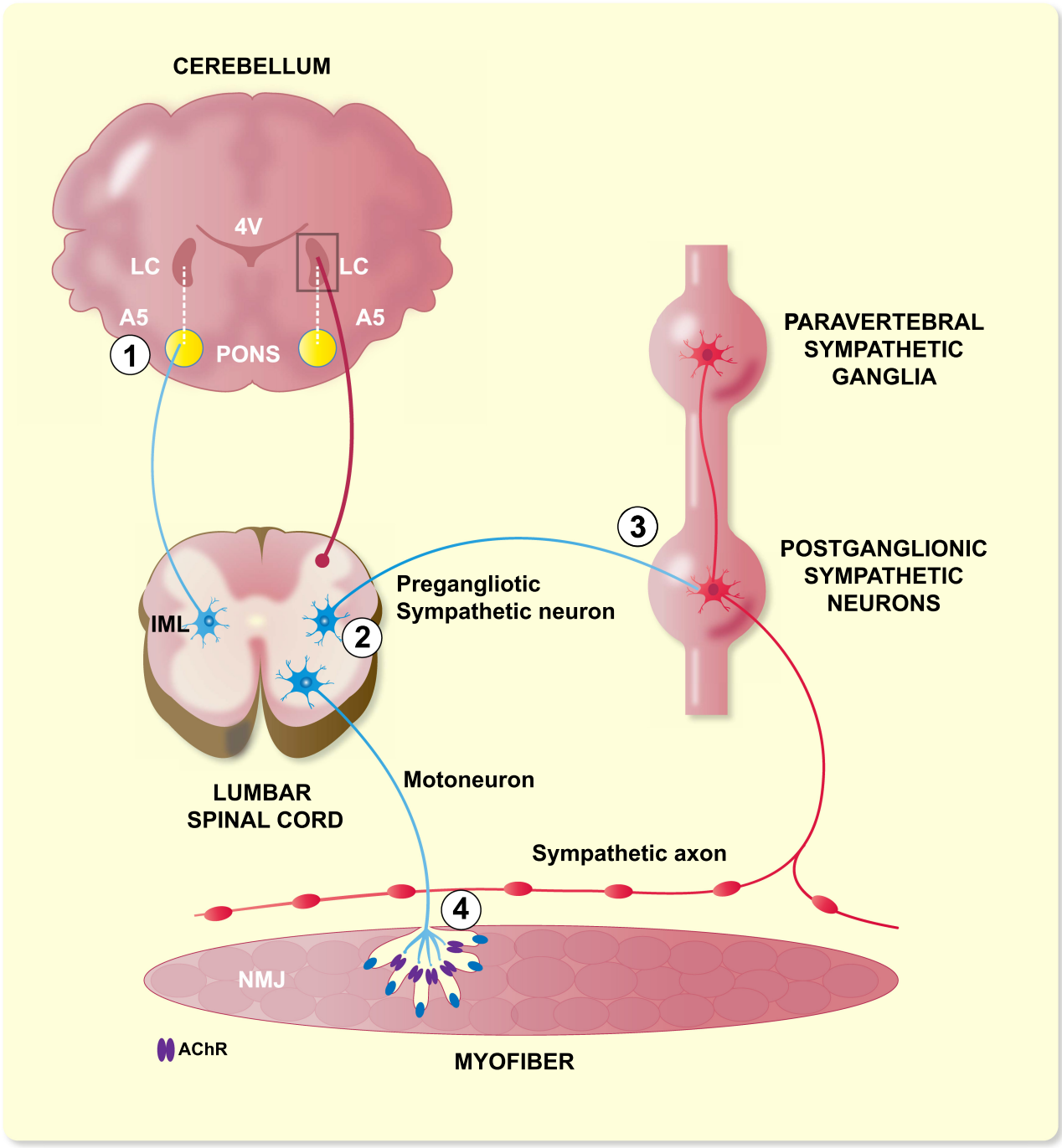

FIGURE 5 Hierarchical organization of central and peripheral noradrenergic and cholinergic neurons that potentially regulate skeletal muscle innervation. Relationship between LC and the spinal cord dorsal horn sensory neurons. Ventrally located A5 noradrenergic neurons ① project to cholinergic pre-ganglionic neurons located at the spinal cord IML ②. The sympathetic pre-ganglionic neurons at the IML synapse with paravertebral sympathetic post-ganglionic neurons ③, which in turn innervate the myofiber ④. Sympathetic neuron axons display periodic bulbous enlargements also known as varicosities. The diagram shows both the sympathetic and motor innervation of the skeletal muscle fiber. Adapted from Ref. [45]

their conduction velocity ranges from 0.2 to 3.3 m/s in the rat,[95–97] while their discharge frequency oscillates widely (0.05–10 Hz).[98] The topographic specificity of innervation and reinnervation in the sympathetic system indicates that pre-ganglionic axons have stable segment-specific identities that influence their connectivity,[99] being muscle innervation an example of segmental matching.[100] Retrograde transneuronal labelling showed specific target assignments for pre-ganglionic neurons.[101]

Electrophysiological analysis in HB9-eGFP transgenic mice on post-natal days 3–9 concluded that the IML contains 4 subpopulations of pre-ganglionic

neurons with different membrane properties, which suggests they have different functions.[102] Histological analysis showed that the number of synapse contacts that spinal cord pre-ganglionic neurons establish with post-ganglionic neurons varies by host species ranging from a 1:15 ratio in the rat to 1:200 in humans.[103] However, the functional role of pre-ganglionic neurons is not well-defined. Additionally, the activity of groups of pre-ganglionic neurons through gap junction coupling[104,105] can produce rhythmic and coordinated rather than selective activity. In light of the pivotal role pre-ganglionic neurons may play in conveying central noradrenergic neuron commands to post-ganglionic neurons,[106] the analysis of the response of various targets to specific pre-ganglionic stimulation must be examined in a physiological experiment. A retrograde viral vector, carrying ChR2 expression in pre-ganglionic neurons by a choline acetyltransferase promoter (ChAT-ChR2[H134R]-EYFP),[107] can be used to elucidate the ability of specific sets of neurons to trigger specific peripheral responses.

7 | PATHOLOGICAL ALTERATIONS IN CENTRAL NORADRENERGIC NEURONS WITH AGEING AND NEURODEGENERATION

Because of the lack of information about A5 in the context of AD, the following discussion focuses on the information on LC. AD, the most prevalent form of dementia worldwide, affects approx. 50 million people and is expected to affect 150 million by 2050.[108,109] Although research has defined some mechanisms, treatment efforts have failed, possibly because by the time cognitive impairment can be clinically observed, neuron loss is irreversible. Interventions designed to reduce noradrenergic neuron vulnerability might target the development of cell hyperactivity and excessive noradrenergic transmission.[81,110–112] Cell loss in the LC is a better predictor of cognitive symptoms than degeneration in other brain regions.[113] Adrenoceptor antagonists, or chemogenetic/optogenetic silencing, could retard AD spread from the brainstem.[111,114] Once the pathology has spread throughout the brain, therapies that increase noradrenergic transmission (e.g., chemogenetic/optogenetic facilitation, noradrenergic prodrugs/agonists/re-uptake inhibitors) could retard cognitive decline if the noradrenergic receptors in brain targets and the cell signaling associated with G-protein-coupled receptors are preserved. Early detection of biological alterations and identification of their mechanisms will drive improved therapeutic approaches.

AD patients' autonomic failure is manifest in orthostatic hypotension dizziness, syncope, and significantly high morbidity.[115–117] Sympathetic nervous system failure is common in old age[118] and neurodegenerative diseases[119] that impair adaptation to common physiological stressors. In the early stages, AD pathology affects brain areas that are important for central autonomic control.[120–123] Hyperphosphorylated tau—a "pretangle" form of the protein that is prone to aggregation—can be detected in the brainstem during the first decades of life, before it appears in the brain (Braak preclinical stage).[124–131] LC neurons show tau phosphorylated at serine 202 and threonine 205 at this stage. Before neurofibrillary tangle formation and after Ser208 phosphorylation[132] tau deposits redistribute from the axon to the soma and dendrites (Figure 6). Braak et al reported that tau lesions reexamined in 2332 non-selected autopsy cases ranging in age from 1 to 100 years, showing that pretangles restricted to subcortical sites were seen mainly at younger ages. The first plaques occurred in the neocortex after the onset of brainstem tauopathy. Plaques generally increased throughout life starting in the 40s. The authors suggested that tauopathy associated with sporadic AD may begin earlier than previously thought and possibly in the lower brainstem rather than in the transentorhinal region.[124,133] Note that AD patients can lose up to 50% of their rostral LC cells.[134] Intra-neuronal lesions associated with AD occur before puberty or in early adulthood and most often affect the noradrenergic projection neurons of the LC.[125] In the pretangle stage of AD pathology, known as *Braak pretangle stages a, b, and c*, phosphor-tau immunoreactivity appears in various areas of LC neurons,[124] while in other brainstem noradrenergic neurons deposits have not been reported, which demands further investigation. Chemogenetic attenuation of neuronal activity in the entorhinal cortex reduces Aβ and tau pathology in the hippocampus,[114] while the same intervention in the LC restores reversal learning in a rat model of AD,[111] and reconfigures the LC functional connectome.[135] Determining whether one noradrenergic neuron subpopulation is more susceptible than another to protein deposition and cell death will help us to detect neurodegeneration at an early stage and establish a prognosis.

8 | CONCLUSIONS

Brainstem noradrenergic neurons form a node integrating many efferents projecting to distinct areas such as those regulating cognition and skeletal muscle structure and function and receive dissimilar afferents through established circuits to coordinate organismal responses to diverse challenges. Genetic lineage tracing analysis shows that brainstem noradrenergic neurons exhibit remarkable

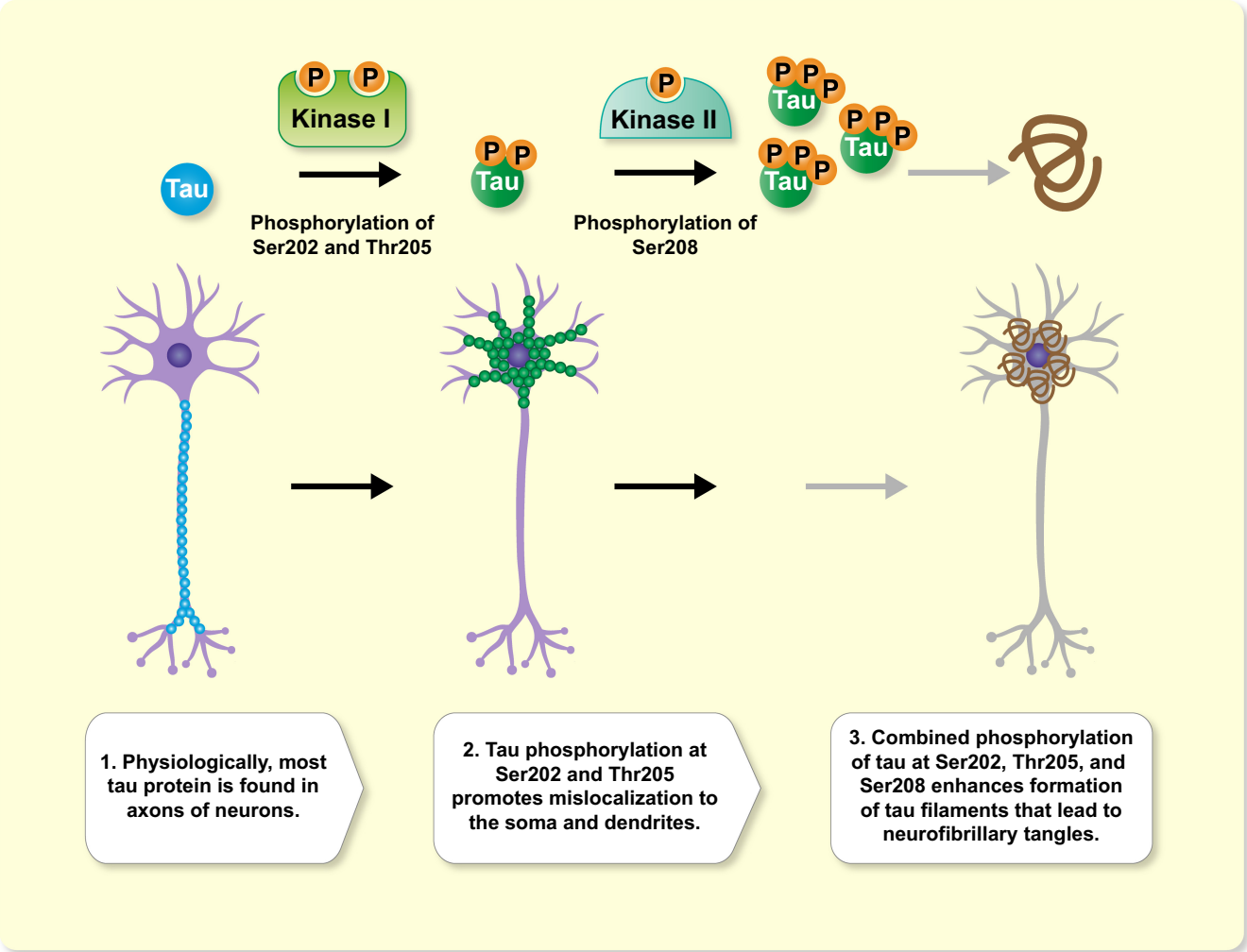

FIGURE 6 Triple phosphorylation of Ser202, Thr205, and Ser208 promotes tau mislocalization and aggregation, leading to NFT formation. (1) Physiological tau protein distribution in neuronal axons. (2) Tau phosphorylation at Ser202 and Thr205 leads to tau redistribution to the soma and dendrites. (3) Tau phosphorylation at Ser202, Thr205, and Ser208 induces the formation of tau filaments and neurofibrillary tangles. Adapted from Ref. [132]

heterogeneity,[48] which may be the substrate for their dissimilar functions. Whether this neuronal heterogeneity dissipates with ageing and/or neurodegeneration, rendering specific neuronal subpopulations more susceptible to cell death or misfolded protein deposits is unknown, but must be evaluated in young, adult, and old mammalian specimens.

Peripheral post-ganglionic noradrenergic neurons innervate skeletal muscle fibres and maintain the integrity of skeletal muscle composition and function at the pre- and post-synaptic NMJ in health and disease.[22,25,136,137] We do not know whether the age-dependent decline in central autonomic neuron cluster composition and/or function accounts for skeletal motor denervation and sarcopenia.

A decrease in LC neuron density is associated with impaired mobility in older adults, indicating that central sympathetic relays may play a critical role in physical activity.[71] Whether those neuronal groups that densely project to the IML influence mammalian skeletal muscle innervation and trophism is an open question for future research on the mechanisms of age-, and neurodegeneration-related sarcopenia.

Sympathetic nervous system impairment leads to skeletal muscle motor denervation.[22,25,87,138] Sympathetic neurons innervate skeletal muscle fibres[22,25,136,139–145] and regulate their metabolism,[73,74,146–148] and neuromuscular transmission in rodents.[22] However, whether pathological alterations to dense, spinally projected neuron groups, such as A5, accelerate AD sarcopenia is unknown.

We must examine how these neurons interact with the LC, skeletal muscle sympathetic innervation, NMJ protein composition and transmission, and myofibre motoneuron innervation by spinal cord pre-ganglionic

neurons over time and with neurodegeneration to determine their effect on memory and cognition. Complex, multidisciplinary approaches, including genetic tracing, specific circuit labelling, opto- and chemogenetics, electrophysiology, and single-cell transcriptomics and proteomics, are required to examine whether sarcopenia may predict cognitive decline and indicate the appropriate time to examine blood and spinal fluid markers and start AD interventions to reduce central noradrenergic neuron hyperactivity.

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CONFLICT OF INTEREST

The author declares that he has no conflicts of interest.

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