Central CO₂ chemoreception and integrated neural mechanisms of cardiovascular and respiratory control

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Guyenet PG, Stornetta RL, Abbott SB, Depuy SD, Fortuna MG, Kanbar R. Central CO₂ chemoreception and integrated neural mechanisms of cardiovascular and respiratory control. J Appl Physiol 108: 995–1002, 2010. First published January 14, 2010; doi:10.1152/japplphysiol.00712.2009.—In this review, we examine why blood pressure (BP) and sympathetic nerve activity (SNA) increase during a rise in central nervous system (CNS) PCO₂ (central chemoreceptor stimulation). CNS acidification modifies SNA by two classes of mechanisms. The first one depends on the activation of the central respiratory controller (CRG) and causes the much-emphasized respiratory modulation of the SNA. The CRG probably modulates SNA at several brain stem or spinal locations, but the most important site of interaction seems to be the caudal ventrolateral medulla (CVLM), where unidentified components of the CRG periodically gate the baroreflex. CNS PCO₂ also influences sympathetic tone in a CRG-independent manner, and we propose that this process operates differently according to the level of CNS PCO₂. In normocapnia and indeed even below the ventilatory recruitment threshold, CNS PCO₂ exerts a tonic concentration-dependent excitatory effect on SNA that is plausibly mediated by specialized brain stem chemoreceptors such as the retrotrapezoid nucleus. Abnormally high levels of PCO₂ cause an aversive interoceptive awareness in awake individuals and trigger arousal from sleep. These alerting responses presumably activate wake-promoting and/or stress-related pathways such as the orexinergic, noradrenergic, and serotonergic neurons. These neuronal groups, which may also be directly activated by brain acidification, have brainwide projections that contribute to the CO₂-induced rise in breathing and SNA by facilitating neuronal activity at innumerable CNS locations. In the case of SNA, these sites include the nucleus of the solitary tract, the ventrolateral medulla, and the preganglionic neurons.

central chemoreceptors; cardiorespiratory integration

A rise in central nervous system (CNS) PCO₂ (central chemoreceptor stimulation) increases breathing, blood pressure (BP), and sympathetic nerve activity (22, 96). Beyond a certain level, CNS PCO₂ also produces arousal from sleep (9, 82) and elicits a conscious sensation that is perceived as aversive in the awake state (69). In this short review we consider how a rise in CNS PCO₂ activates the circulation. The focus is on the primary response of the vasomotor sympathetic system to central chemoreceptor stimulation (the central sympathetic chemoreflex, CSC). The parasympathetic control of the heart and the secondary circulatory reflexes that result from changes in pulmonary ventilation are not discussed.

As a preamble, it may be useful to recall that the brain performs two interrelated tasks that are critical to circulatory control. The first one is BP stabilization. This function is largely independent of breathing intensity and relies primarily on the arterial baroreflex with an important contribution of vestibular/cerebellar mechanisms in larger mammals. These mechanisms protect the brain and other sensitive organs against hypotension/hypoperfusion that could potentially result from postural changes, fluid loss, or excessive muscle vasodilatation during exercise. The second task, which is highly integrated with breathing, is the regulation of tissue perfusion. This regulation is behavior dependent and occurs via adjustments of the cardiac output, regulated rises in BP, and differential activation of the sympathetic tone to various organs. Blood gas delivery to the tissues requires that the cardiac output roughly covary with alveolar ventilation. The neural control of the cardiac output (cardiovagal and sympathetic
ROLE OF THE VENTROLATERAL MEDULLA IN VASOMOTOR CONTROL

The rostral ventrolateral medulla (RVLM) is a ventrolateral quadrant of the medullary reticular formation that overlaps with the Bötzinger and pre-Bötzinger subdivisions of the ventral respiratory column defined by respiratory physiologists (3). The RVLM contains a large collection of neurons that innervate the preganglionic sympathetic neurons (SPGNs) monosynthetically (presympathetic neurons) (Fig. 1A). These neurons are an important convergence point for sympathetic reflexes elicited by cardiopulmonary receptors and descending inputs from the hypothalamus and higher in the neuraxis (28). The presympathetic neurons of the RVLM are presumably glutamatergic (71, 99), but a large subset of them, defined as C1 neurons, also express the entire complement of catecholamine-biosynthetic enzymes inclusive of the epinephrine-producing phenylethanolamine N-methyl transferase (PNMT) (35, 88). In addition, the presympathetic neurons differentially express several neuropeptides such as substance P, enkephalin, and neuropeptide Y (56). The C1 neurons are not exclusively presympathetic as many C1 cells do not innervate sympathetic preganglionic neurons but target instead the hypothalamus, basal forebrain, and periaqueductal gray matter. These rostrally projecting neurons contribute to the neuroendocrine and autonomic responses to somatic stresses such as hypotension, hemorrhage, nociception, and infection (28, 90). RVLM presympathetic neurons are functionally as well as neurochemically heterogeneous. A subset of these neurons seems to regulate skeletal muscle vascular beds preferentially whereas other subsets probably regulate primarily the splanchnic circulation, the heart, the kidney, and so on. This arrangement, defined as “organotopy,” presumably underlies the ability of the RVLM to differentially regulate the cardiac output, BP, and organ perfusion (65).

The presympathetic neurons of the RVLM are very active at rest in vivo (11). This characteristic is attributed to a combination of intrinsic properties (autoactivity) and synaptic drives (28, 45, 58). Under most anesthetics, the activity of the presympathetic neurons is very high (up to 35 Hz), presumably because of the depressant effect of these drugs on their main source of inhibition, the CVLM (Fig. 1A). The excitatory drives unmasked by this disinhibition are not mediated to a substantial degree by conventional ionotropic glutamatergic transmission (28). Their exact location and the nature of the participating transmitters are unknown. This mystery is a major limitation to current understanding of BP control in health and disease. In anesthetized rodents, the bulk of the activity of sympathetic nerves and of the RVLM presympathetic neurons persists under hypoxia and at extremely reduced levels of PCO2; therefore this basal activity is clearly not dependent on central or peripheral chemoreceptor tone nor does it depend on an active central respiratory network. Human SNA likewise persists in the complete absence of respiratory activity (e.g., 97).

Massive increases in sympathetic tone occur in response to even slight decreases in systemic BP (28, 104). This sympathetic “reserve” is independent of the activity of the central sympathetic “reserve” is independent of the activity of the central respiratory network and probably results from the dishinhibition of the RVLM presympathetic neurons rather than from an increase in their excitatory drive. This “reserve” underlies the BP stabilization role of the RVLM and has probably little to do with cardiorespiratory integration per se although, as will be seen later, both regulations may converge through a common pool of GABAergic interneurons that keeps the activity of
RVLM presympathetic neurons in check at all times. This inhibitory input originates from interneurons located more caudally within a region of the VLM called the caudal ventrolateral medulla (CVLM, Fig. 1A) (91, 101, 110). The CVLM is roughly coextensive with the pre-Bötzinger complex and the rostral ventral respiratory group (rVRG) defined by respiratory physiologists (3, 14, 91, 109). The CVLM GABAergic interneurons are driven to a large extent by the ongoing activity of the arterial baroreceptors (Fig. 1A); therefore their firing is highly synchronized with the pressure pulse (43, 91). These neurons probably receive a monosynaptic excitatory input from the second-order cells in the arterial baroreflex pathway, which reside in the dorsolateral region of the caudal solitary tract nucleus (NTS) (8, 109). The NTS-CVLM-RVLM-SPGN pathway (Fig. 1A) is considered crucial to the operation of the sympathetic baroreflex, hence to the short-term stability of BP (28).

OTHER PATHWAYS THAT CONTROL VASOMOTOR SNA

The RVLM is not the only source of innervation of the SPGNs that control the circulation. These SPGNs also receive prominent innervation from spinal interneurons, the midline medulla oblongata (including from serotoninergic neurons), the pontine A5 noradrenergic cell group, the dorsolateral pons, and the hypothalamus (42). Hypothalamic inputs include projections from the paraventricular nucleus and from the orexigenic neurons of the perifornical region (42, 59).

Several of these structures (the cord, the midline medulla oblongata, perhaps even the paraventricular nucleus of the hypothalamus) are sources of fast synaptic inputs to the SPGNs (ionotropic GABA, glutamate or glycine synapses) (30, 50, 98). Other regions such as the raphe, the A5 cell group, and the paraventricular nucleus of the hypothalamus are also, or predominantly (A5, raphe), sources of metabotropic transmitters (serotonin, norepinephrine, vasopressin, oxytocin, orexin) (28, 41, 42). These transmitters alter the intrinsic properties of the SPGNs, causing, among other effects, large changes in their accommodation to repetitive stimuli, which presumably modulate (amplify or attenuate) the efficacy of the conventional ionotropic receptor-mediated synapses (e.g., 37, 38).

THE CENTRAL RESPIRATORY NETWORK AS INTERFACE BETWEEN CENTRAL CHEMORECEPTORS AND THE SYMPATHETIC OUTFLOW

A rise in CNS PCO2 increases sympathetic nerve discharge and BP in anesthetized and awake animals, and in humans (67, 79, 95). The sympathoactivation occurs in waves that are synchronized with the central respiratory cycle (31, 67). The respiratory pattern of SNA is very similar regardless of whether central or peripheral chemoreceptors are being activated. This respiratory pattern is species specific and, within a given species, varies between different functional classes of sympathetic efferers (40). For example, in rats the respiratory pattern of the sympathetic nerves that target splanchnic vessel beds is generally different from that of the sympathetic efferents to the skeletal muscle vasculature (31, 78). These characteristics suggest that an increase in central respiratory drive caused by central chemoreceptor stimulation may exert a nonuniform influence over the various vascular beds, the heart, etc. Similar observations have been made with respect to the influence of peripheral chemoreceptors on the various sympathetic outflows (64).

THE PRESYMPATHETIC NEURONS OF THE RVLM AS PRINCIPAL RELAY OF THE CSC

In anesthetized adult rats subjected to a bilateral vagotomy and section of the four buffer nerves (aortic nerves and carotid sinus nerves), a procedure that eliminates input from arterial baroreceptors, cardiopulmonary receptors, and peripheral chemoreceptors, the discharge rate of the RVLM presympathetic neurons increases in parallel with SNA and to a comparable degree (70). Furthermore, the activation of these RVLM neurons is patterned by the central respiratory cycle in the same differentiated manner as the SNA (32, 63, 70). Thus, under anesthesia, the RVLM presympathetic neurons undoubtedly contribute to the sympathoactivation caused by CNS acidification. The simplest explanation of the phenomenon would be that CNS acidification activates subsets of respiratory neurons that, in turn, excite the RVLM presympathetic neurons (Fig. 1A, arrowhead 2). Connections between respiratory neurons of the Bötzinger region and RVLM presympathetic cells have been proposed, but the supportive evidence remains preliminary (102). Connections between the dorsal pons and the ventral respiratory column (Fig. 1A) are essential to the generation of the three-phase “eupneic” respiratory pattern (93). These connections are also necessary for the respiratory modulation of SNA (7). Unfortunately, this observation does not clarify the location of the respiratory neurons that are immediately antecedent to the RVLM vasomotor neurons because the dorsolateral pons innervates every medullary region involved in respiratory control and the connections are reciprocal.

THE CVLM NEURONS AS INTERFACE BETWEEN THE RESPIRATORY NETWORK AND THE SYMPATHETIC OUTFLOW

The CVLM neurons (Fig. 1A) rather than the RVLM presympathetic neurons may be the main interface between the respiratory network and the network that generates the vasomotor SNA. One argument is that of proximity. The CVLM neurons are located within the pre-Bötzinger and rVRG segments of the ventral respiratory column, which are most critical to define the respiratory rate and inspiratory amplitude. However, the principal evidence is that the discharge of the CVLM GABAergic interneurons is not driven just by the ongoing activity of the baroreceptors but it is also very powerfully modulated by the central respiratory network (61). The respiratory modulation of the CVLM neurons is phase-spanning in rats and occurs in many different patterns (61). Several of these respiratory patterns are the mirror image of those displayed by subsets of RVLM neurons and sympathetic efferents. Given that CVLM neurons are the main known source of inhibitory input to the RVLM neurons, the complementary nature of these respiratory patterns suggests that the respiratory fluctuations of the discharges of RVLM neurons and sympathetic efferent could largely originate from the respiratory gating of the baroreflex at the CVLM level (Fig. 1A, arrowhead 1).
THE NUCLEUS OF THE SOLITARY TRACT AS INTERFACE BETWEEN THE RESPIRATORY NETWORK AND THE SYMPATHETIC OUTFLOW

In theory, the central respiratory gating of the baroreflex could also occur upstream of the CVLM neurons on the sensory side, namely within the nucleus of the solitary tract (NTS), which provides the baroreceptor-related excitatory drive to the CVLM neurons (Fig. 1A, arrowhead 3). The evidence supporting this view is equivocal.

The NTS contains many neurons with respiratory-related activity, and this structure is innervated by neurons with central respiratory modulation (8, 51, 109). The NTS also contains a plethora of neurons that respond to the mass activation of arterial baroreceptors (20, 80, 81, 86, 113), and some of these neurons do have a respiratory modulation (66). However, the evidence that these dual (baroreceptor and respiratory) input neurons contribute to the sympathetic baroreflex is slim for the following reason. Robust pulse modulation is present on the sensory afferent side (baroreceptors) and at every step of the sympathetic baroreflex pathway beyond the NTS (CVLM, RVLM, sympathetic pre- and postganglionic neurons). Yet, virtually none of the NTS barosensitive neurons that have been recorded exhibit a pulse-modulated discharge (e.g., 89). These barosensitive NTS neurons are therefore unlikely to be those that mediate the sympathetic baroreflex because no known mechanism can account for the disappearance of the pulse modulation within the NTS and its reappearance downstream in the baroreflex pathway. Thus the question of whether the baroreflex is modulated by the central respiratory pattern generator at the level of the NTS is still unanswered.

The NTS contains neurons that respond directly to acid in vitro and may also detect changes in PCO2 in vivo (18, 74). These neurons have not been characterized from a functional and connectivity standpoint but the observation suggests that, in theory, CO2 could also regulate the sympathetic outflow at the level of the NTS.

The primary cardiovascular responses elicited by activation of central or peripheral chemoreceptors are modified to a considerable extent by the resulting changes in pulmonary ventilation (17, 96). The NTS presumably plays a critical role in these secondary circulatory reflexes. This important topic is not within the scope of this review.

RESPIRATORY NETWORK-INDEPENDENT STIMULATION OF THE SYMPATHETIC TONE BY BRAIN ACIDIFICATION

The respiratory gating of the CVLM neurons does not entirely explain the CSC for two reasons. First, it is not clear that this gating results in an increase or a decrease in the mean activity of the CVLM neurons. Second, silencing the pre-Bötzinger/rVRG/CVLM region with injections of the GABA-mimetic muscimol increases the sympathoexcitatory elicited by central (or peripheral) chemoreceptor stimulation (48, 70). If the CSC was entirely caused by disinhibition of the RVLM, this reflex should have been reduced or eliminated, not increased, by silencing the CVLM region because muscimol injection into this region silences the respiratory network and eliminates the baroreflex (49, 111). After silencing the CVLM region, chemoreceptor stimulation produces a seemingly aperiodic (tonic) activation of SNA consistent with the elimination of the central respiratory drive (48, 70). This evidence suggests that brain acidification influences the sympathetic outflow in two ways. The first depends on the degree of activation of the central respiratory network and probably involves the gating of the baroreflex at the level of the CVLM. This mechanism presumably accounts for the respiratory synchrony of the sympathetic bursts evoked by chemoreceptor stimulation. CNS acidification is also capable of activating the sympathetic vasomotor tone via pathways that are independent of the central respiratory network. Consistent with this notion CO2 can activate the sympathetic outflow at partial pressures that are well below the apneic threshold in some in vivo preparations (107) and, in awake humans, SNA increases before a respiratory motor output can be detected as CO2 rises during posthyperventilation apnea (97). These observations, both in animals and in humans, support the existence of a line of communication between central chemoreceptors and the sympathetic network that bypasses the respiratory rhythm and generating network.

ARE THE RVLM PRESYMPATHETIC NEURONS ACID SENSITIVE?

This hypothesis would explain very simply why increasing brain PCO2 activates SNA even when the respiratory network is silenced. To test it, we recorded from RVLM presympathetic neurons of the C1 variety in brain slices from a tyrosine-hydroxylase-EGFP transgenic mouse (62) and we examined whether the activity of these neurons changes during acidification of the slice in the 6.9–7.5 pH range. The C1 cells have similar properties in mice as in rats of the same age (6–9 day old), namely a slow regular discharge rate (1.8 ± 0.3 Hz) and a profound inhibitory response to bath application of an α2-adrenergic agonist (57). The spontaneous discharge rate of the RVLM catecholaminergic neurons of the mouse was unaffected by acidification (54). Under the same experimental conditions (age, temperature, perfusion medium) the retrotrapezoid neurons of the mouse exhibited a robust response to acidification (0–5 Hz between pH 7.8 and 7.0) (54). Based on this evidence, the C1 neurons are unlikely to function as central chemoreceptors and their activation by hyperoxic hypcapnia in vivo is presumably mediated by synaptic inputs. This interpretation is subject to several caveats: the C1 cells are only a subset of the RVLM presympathetic neurons, albeit a large one (>70%), and these cells were studied at room temperature and, for technical reasons, in 6- to 10-day-old mice. In rats at least, the central chemoreflex is at a low ebb during this period of life although this phenomenon may not be caused by a major change in the pH sensitivity of individual brain neurons (100).

THE RETROTRAPEZOID NUCLEUS AS A PUTATIVE SOURCE OF CHEMORECEPTOR INPUT TO THE SYMPATHETIC OUTFLOW

The tonic activation of SNA caused by hypcapnia in the absence of central respiratory drive suggests that CO2 can be detected by CNS neurons that are not part of the respiratory rhythm and pattern generator and respond to CO2 in a tonic fashion when the respiratory network is silenced. Retrotrapezoid nucleus (RTN) neurons (Fig. 1B) are examples of neurons that fit this requirement. These cells are activated by hypcapnia in vivo (72), many of them have a CO2 threshold below that of the respiratory network, and they display several
types of phase-spanning respiratory modulation when the respiratory network is strongly activated (10, 29, 75) but their CO₂-induced discharge is tonic at low levels of CO₂ or when the respiratory network is silenced by inhibition of the pre-Bötzinger/rVRG region (106). These glutamatergic neurons drive the respiratory rhythm and pattern generator (1). They innervate the entire ventrolateral medulla, which includes the ventral respiratory column and the regions that are especially critical to sympathetic tone generation such as the CVLM and the RVLM (1, 87). The diversity of phase-spanning respiratory patterns displayed by RTN neurons (in rats) could also, in theory, account for the variety of respiratory patterns exhibited by CVLM neurons in the same species (29, 61). Although RTN neurons have properties suited to contribute to the activation of the sympathetic tone by low levels of brain Pco₂, the evidence supporting this theory is still modest.

THE WAKE-PROMOTING SYSTEMS AS ALTERNATE SOURCES OF CENTRAL CHEMORECEPTOR INPUT TO THE SYMPATHETIC OUTFLOW

Serotonergic, orexinergic, and noradrenergic neurons are wake-ON neurons that innervate the entire brain stem respiratory network down to the motor neurons (5, 39, 52). The state-dependent activity of these neurons most likely contributes to the “waking neural drive to breathe,” the brain mechanism that maintains breathing during waking regardless of the CO₂ level (2, 76, 83, 92). These wake-ON neurons are activated by high levels of hypercapnia (25, 44, 103), presumably for several reasons. First, when brain Pco₂ reaches levels that cause aversive sensations and/or arousal (9, 69, 82), many if not all the executive pathways involved in arousal are presumably recruited to some degree. Second, orexin neurons appear to be essential for the cardiorespiratory responses to stress and emotions (53) and severe hypercapnia is an especially aversive stimulus (69). Finally, subsets of serotonergic, catecholaminergic, and orexinergic neurons may also have central chemoreceptor properties (18, 19, 26, 34, 55, 74). Given that these three neuronal systems also target virtually all the CNS sites involved in generating the sympathetic tone (42, 52), their contribution to the sympathetic component of the central chemoreflex is plausible a priori.

Orexinergic neurons, for example, innervate sympathetic preganglionic neurons and the presympathetic neurons of the RVLM and, at both sites, orexin exerts effects that somehow result in an increase in sympathetic tone (4, 15, 16, 23, 27, 94). Furthermore, orexin knockout (KO) mice are markedly hypotensive when awake (46). In addition, the respiratory component of the central chemoreflex is attenuated in orexin KO mice only during the period when orexin neurons are active, i.e., during waking hours (19). This observation could have several potential explanations, one of which being that orexin causes a widespread increase in the excitability of brain stem neurons, including the central respiratory controller, motor neurons, and the RTN, thereby potentiating the effect of brain stem acidification on breathing regardless of where the chemoreceptors are located (21). A second possibility is that the orexin neurons might be themselves activated by acidification. This notion is supported by experiments in vitro (19, 24, 112) but requires verification in vivo. Indeed, the in vitro pH sensitivity of orexin neurons is attributed to the presence of a TASK-like resting potassium conductance (24, 112), but TASK channel knockout produces no effect on the CRC (73). In addition, only a very small proportion of orexin neurons express c-Fos in mice exposed to as much as 10% CO₂ (103). This result could mean that, in apparent contradiction with the in vitro data, only a very small subset of orexin neurons responds to acidification in vivo. It could also mean that the orexin neurons are not directly affected by Pco₂ in vivo and that their mild activation by hypercapnia denotes the aversive and wake-promoting effect of this stimulus. Indeed, Fos expression by orexin neurons normally tracks the level of vigilance (60). Finally, the orexin neurons also activate the serotoninergic system and the pontine noradrenergic neurons, which could indirectly change the activity of the sympathetic outflow (12, 36, 47).

Given the ubiquitous presence of serotonergic terminals in the lower brain stem and elsewhere, an equally large range of mechanisms could contribute to the known facilitation of the CRC by serotonergic neurons (34) and the increase of serotonin release caused by hypercapnia (44). One possibility is that specialized subsets of serotonergic neurons are directly activated by brain acidification in vivo. Many lower brain stem serotonergic neurons are indeed activated by acidification in vitro (84, 85), and a small subset of midline raphe, putatively serotonergic, neurons (25%–25%) respond to hypercapnia in conscious cats (108). However, other subsets of serotonergic neurons including parapyramidal neurons with proven projections to the intermediotegmental cell column are unresponsive to CO₂ under anesthesia and therefore unlikely to be directly acid sensitive in vivo (72).

The pontine noradrenergic neurons of the locus ceruleus (LC) are modestly activated by severe hypercapnia in vivo (25, 33). This effect probably results from their intrinsic sensitivity to acid (26, 77) and from synaptic inputs. Indeed, the LC is innervated by C1 neurons and by the orexin system, which are CO₂ responsive in vivo (36, 68, 70). The LC is not known to directly target the spinal and brain stem circuits that generate the sympathetic tone or the respiratory outflows and, under specific anesthetic conditions, LC stimulation even lowers BP (105). However, LC neurons have a very wide array of brain projections and are also activated by arousing stimuli (6). In that general sense the LC could potentially contribute to the rise in sympathetic tone caused by hypercapnia, especially if the stimulus is intense enough to be aversive and wake-promoting. The pontine A5 noradrenergic neurons selectively target the central circuitry that generates the sympathetic outflow (13, 42). These neurons have intrinsic properties that are very similar to those of the LC. Their acid sensitivity has not been investigated, and their pattern of activity in the absence of anesthesia remains unexplored.

CONCLUSIONS

Central chemoreceptors influence the sympathetic outflow via their effects on the central respiratory network and independently of it. A modest rise in CNS Pco₂ increases sympathetic vasomotor tone in bursts that are synchronized with the central respiratory cycle. This synchronization occurs at least in part via a periodic respiratory gating of the baroreflex, which happens at the level of the CVLM or, possibly, within the NTS. This effect results in a respiratory synchronous disinhibition of the presympathetic neurons located in the RVLM. The same or
different central chemoreceptors also contribute to the rise in SNA caused by CNS acidification in ways that are independent of their effects on the respiratory network. Some of these chemosensitive neurons are evidently responsive to small changes in PCO2 around the normal resting level of 40 mmHg. These neurons are not definitively identified but candidates include the retrotrapezoid neurons or neurons located within the NTS or the raphe. Many other brain neurons are activated by CO2 but, presumably, only in a range of concentration that triggers averse sensations in the waking state and arousal from sleep. Their activation by CO2 may be partly network driven and partly due to an intrinsic sensitivity to acid. These neurons probably contribute to the increase in sympathetic tone associated with defensive mechanisms that restore breathing when the airways are obstructed. The LC, the serotonergic system, and the orexin neurons could be in this second category.

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DISCLOSURES
No conflicts of interest are declared by the authors.

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