HIGHLIGHTED TOPIC | Reflexes from the Lungs and Airways

Plasticity in the nucleus tractus solitarius and its influence on lung and airway reflexes

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Bonham, Ann C., Chao-Yin Chen, Shin-ichi Sekizawa, and Jesse P. Joad. Plasticity in the nucleus tractus solitarius and its influence on lung and airway reflexes. J Appl Physiol 101: 322–327, 2006. doi:10.1152/japplphysiol.00143.2006.—The nucleus tractus solitarius (NTS) is the first central nervous system (CNS) site for synaptic contact of the primary afferent fibers from the lungs and airways. The signal processing at these synapses will determine the output of the sensory information from the lungs and airways to all downstream synapses in the reflex pathways. The second-order NTS neurons bring to bear their own intrinsic and synaptic properties to temporally and spatially integrate the sensory information with inputs from local networks, higher brain regions, and circulating mediators, to orchestrate a coherent reflex output. There is growing evidence that NTS neurons share the rich repertoire of forms of plasticity demonstrated throughout the CNS. This review focuses on existing evidence for plasticity in the NTS, potential targets for plasticity in the NTS, and the impact of this plasticity on lung and airway reflexes.

airways; synaptic excitability; intrinsic excitability; brain stem; cough

PLASTICITY

Most synapses have a rich repertoire of plasticity targets and modes. Plasticity can affect single to multiple afferent synapses onto the neuron and have short-term (milliseconds to minutes) to long-term (minutes to days) effects. Plasticity can affect synaptic or intrinsic neuronal properties: synaptic plasticity through presynaptic events could change the probability of release of the principle neurotransmitter, result in the release of other neurochemicals stored in the presynaptic neuron that are not normally released, or shift the balance of the multiple inhibitory and excitatory modulatory inputs that determine the synaptic excitability. Dynamic plasticity through postsynaptic events could change the number, affinity, distribution, or availability of neurotransmitter or neuromodulator receptors, their subunits, or their downstream signaling pathways. Intrinsic plasticity could change the excitability of the neuron by modifying the expression, trafficking, or function of one or more ion channels or their subunits that define the intrinsic neuronal excitability (10, 24, 33). Hebbian plasticity, the classic activity-dependent plasticity, associates the firing pattern of the presynaptic partner with the postsynaptic partner to elicit changes (strengthening or weakening) of the output of a specific synapse. Hebbian plasticity is a positive-feedback process, inasmuch as effective synapses are strengthened, making them more effective, and ineffective synapses are weakened, making them even less effective. This property could destabilize neuronal networks over time by excessively increasing or decreasing the firing pattern of postsynaptic neurons to a maximum or to zero, respectively (1). A key example of Hebbian plasticity is long-term potentiation, which is induced by the correlated firing of the presynaptic and postsynaptic neurons, or high-frequency stimulation of the presynaptic neuron, resulting in a long-term increase in synapse strength at a single synapse. Homeostatic plasticity, by contrast, scales the strengths of all synaptic inputs up or down by changing the responses of the postsynaptic neurons in an attempt to ultimately maintain a stable firing rate of the postsynaptic neurons within a functional range. An example is the work by Turrigiano and Nelson (70, 71) showing that the synaptic output was increased following deprivation of neuronal activity and reduced following an enhancement of neuronal activity, as measured by the fluctuation in the amplitude of miniature excitatory postsynaptic currents. It seems reasonable to assume that this abundant cadre of targets, dimensions, and mechanisms of plasticity may also operate in lung and airway reflex central networks.
NTS, A STRATEGIC SITE FOR PLASTICITY

The NTS is the interface between the sensory airway fibers and all downstream synapses in the lung and airway reflex pathways. The second-order NTS neurons, the first site of synaptic contact, bring to bear their own intrinsic and synaptic properties to integrate the sensory input from the airway nerve fibers with converging inputs from local networks, higher brain regions, and circulating mediators, to orchestrate a coherent reflex output. These synapses undoubtedly have the potential to exhibit the plasticity demonstrated throughout the CNS. Moreover, plasticity at these strategic synapses in the airway reflexes would have the capacity to alter the nature of the reflex output: exaggerating it, prolonging it, suppressing it, or transforming it into some other pattern that is more complex than that created in the absence of plasticity. What are NTS targets of plasticity in the lung and airway reflex circuitry?

PLASTICITY IN PRIMARY AFFERENT NERVES

There is considerable evidence that vagal sensory nerves, including some from the lungs and airways, undergo plasticity in response to exposure to indoor and outdoor pollutants, inflammation, and allergens, all of which can trigger reflex changes in airway tone and evoke cough (14, 15, 72, 74). The plasticity has been shown to manifest as increases in the mRNA, encoding substance P in vagal afferent nerves (34), de novo substance P expression in Aδ vagal afferent cell bodies (57), depolarization of the membrane potential, blockade of an anomalous rectifier (73), and increases in lung vagal Aδ- and C-fiber afferent neuronal excitability (12, 44, 56). These changes in the phenotype and increased excitability may result in an increased sensory traffic to the NTS and/or release of neurochemicals stored in the nerves. Changes, even short-term, in the pattern or frequency of peripheral sensory input might trigger short- or long-term changes in the NTS neurons (28, 32, 42).

NEUROTRANSMITTERS AND NEUROMODULATORS

Glutamate and GABA are ubiquitous excitatory and inhibitory transmitters, respectively, throughout the CNS, and plasticity in glutamatergic and GABAergic systems has been extensively reported (9). In the NTS, glutamate activation of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor is the cornerstone for synaptic transmission between the vagal afferent neurons and second-order NTS neurons (3, 37). However, some second-order NTS neurons also possess functional N-methyl-d-aspartate (NMDA) receptors, which mediate a slower developing, longer lasting component of glutamate signaling. The NMDA receptors likely come into play when the cell is depolarized, such as might occur during high-frequency afferent traffic (2, 5, 27, 58, 63, 65). Activation of the NMDA receptors prolongs the time during which otherwise ineffective inputs can be integrated and can enable the neurons to transduce afferent input, which has no apparent pattern, into patterns. For example, NMDA induces bursting in second-order NTS neurons (67, 68) and converts irregular firing patterns into regular ones (77). NMDA receptors have been shown throughout the CNS to provide a neural substrate for long-term increases in synaptic efficacy (4, 69, 76). More recent work indicates that trafficking, including the stabilization of receptors at the membrane by scaffolding proteins and regulation by kinases and phosphatases, as well as transcription of NMDA receptors or NMDA receptor subunits, may contribute to homeostatic plasticity.

In terms of the NTS, the studies by Aicher et al. (2) show that, within the NTS, 42% of the neurons contacted by vagal afferent terminals contained NMDA receptor R1 immunoreactivity. Interestingly, NMDA R1 labeling was also seen on membranes of vesicular cytoplasmic organelles, suggesting that abundant NMDA protein is available for activity-dependent mobilization to the plasma membrane. The findings provide a rich potential mechanism for plasticity in airway reflexes through NMDA receptor trafficking in the pre- and postsynaptic partners.

The metabotropic glutamate receptors, modulating both glutamate and GABA signaling in the NTS, provide an additional target for plasticity (20, 22, 64). Studies in other networks have demonstrated that activating presynaptic and postsynaptic metabotropic glutamate receptors not only acutely modulates neurotransmission, but also induces Hebbian plasticity: long-term potentiation (60) and long-term depression (8, 35, 40, 49, 66). To the extent that plasticity of metabotropic glutamate receptors on neurons in the lung and airway reflex pathway in the NTS can occur, the data could provide new insights into how the transmission of airway-related information is modified to evoke long-term changes in reflex outputs.

GABA can significantly inhibit synaptic transmission in the NTS (20, 50, 78). There is direct evidence for plasticity in the NTS in the baroreflex pathway. Mei et al. (52) showed that second-order NTS neurons in the baroreflex pathway, which are only modestly sensitive to inhibitory influences by GABAergic inputs in the normotensive state, become exquisitely sensitive after 4 wk of renal hypertension. Their data indicate a plasticity of the inhibitory synaptic input to second-order neurons, which would profoundly change the output of the cardiovascular sensory input and provide proof of principle for plasticity to occur at airway-CNS synapses.

In addition to the neurotransmitters, glutamate and GABA, there is a considerable body of literature on the role of neuromodulators in plasticity in the sensory and motor cortex (39, 53). A number of these neurochemicals have been identified in the NTS and have been shown to modulate neuronal activity, thus forming powerful and diverse targets for plasticity in the NTS. Some of the neuromodulators have been directly implicated in modifying synaptic transmission. For example, dopamine acting at D2 receptors (48), adenosine acting at A1 receptors (47), neurotensin (59), serotonin (61), and substance P acting at neurokinin 1 (NK1) receptors (64) modify glutamate release, whereas neurotensin (59) and glutamate acting at metabotropic glutamate receptors (20) also modify GABA release. Because the neurochemicals are for the most part synthesized in the cell bodies of the vagal neurons (41), it is tempting to speculate that, under certain conditions, they can be transported centrally to the terminals in the NTS for release. Long-term changes in their synthesis or release could provide long-term changes in synaptic transmission and hence lung and airway reflex outputs. Thus plasticity in heterosynaptic regulation could produce long-term changes in the...
delicate balance of the primary excitatory and inhibitory inputs to the NTS neurons. Studies of antitussive agents provide additional insights into the neurochemicals as targets for plasticity in one airway reflex, the cough reflex. The finding that a D2-receptor agonist inhibits the discharge of rapidly adapting receptors and reduces reflex-induced cough in the dog (11) correlates with the actions of D2 agonists in the NTS in reducing glutamate release, as shown by the decrease in frequency of excitatory postsynaptic currents at second-order neurons.

Although there are only limited studies on plasticity in neuromodulator systems in the NTS, the findings implicating plasticity in the expression of substance P in airway afferent fibers raise the possibility that substance P might also be important at NTS synapses. Substance P is found in nerve terminals in the NTS (41), some of which arise from vagal sensory neurons and can act presynaptically at NK1 receptors to modulate the release of glutamate from the central terminals of the vagal sensory neurons onto second-order lung afferent neurons in the NTS (64) or perhaps to be co-released with glutamate to act at postsynaptic sites. Our previous work (45) provided more direct evidence that substance P in the NTS is recruited to contribute to the exaggerated reflex cough in young guinea pigs exposed to second-hand tobacco smoke (SHS). The guinea pigs, exposed to SHS for their first 6 wk of life, exhibited an augmented cough in response to citric acid aerosol evoked by the exposure, did not change the cough evoked in the control group of guinea pigs exposed to filtered air.

CIRCULATING MEDIATORS

In addition to a change in the neural traffic, circulating mediators may contribute to long-term plasticity in NTS neuronal behavior through various pathways (26). First, circulating inflammatory mediators, which stimulate or sensitize the peripheral airway sensory endings, may directly access or indirectly influence the activity of NTS neurons. The adjacent area postrema, the most caudal of the circumventricular organs (6, 19, 75), by virtue of its lack of a blood-brain barrier and its prominent axonal projections to the NTS, provides an anatomical pathway whereby circulating mediators can affect NTS neurons. In this regard, we have previously shown that stimulation of area postrema neurons facilitates NTS neuronal processing of vagal afferent inputs, essentially amplifying the output of the NTS neurons to sensory signals (6, 19). Second, the caudomedial NTS region, where the lung and airway sensory nerves terminate, also lacks a complete blood-brain barrier and features local complexes of fenestrated capillaries and perivascular spaces that afford the NTS neurons direct exposure to blood-borne inflammatory mediators (38). Finally, there is growing evidence that the brain is an immunologically competent and active organ, with a large number of chemokines and chemokine receptors expressed in neurons, astrocytes, microglia, and oligodendrocytes, either constitutively or induced by inflammatory mediators (7). With regard to the NTS, there is suggestive evidence that circulating inflammatory mediators can influence NTS neuronal behavior directly through local synthesis (26, 36, 51).

INTRINSIC EXCITABILITY

Plasticity in the intrinsic properties of neurons through changes in the structure, function, expression, localization, or trafficking of ion channels or their subunits has been demonstrated throughout the CNS (23, 25, 46, 54, 62). A number of ion channels and subunits have been characterized in NTS neurons, including the hyperpolarization-activated current (43), transient outward K+ current (16, 29–31, 55), the delayed outward rectifier (16, 55), and the small conductance, apamin-sensitive Ca2+-dependent K+ current. A previous study in a rhesus monkey model of allergic asthma demonstrated plasticity in NTS neuronal intrinsic activity following extended exposure to allergen. The NTS neurons in the primates exposed to allergen displayed a more depolarized resting membrane potential, an increased input resistance, and a marked increase in spiking activity in response to depolarizing current injections (21).

Fig. 1. Example of homeostatic plasticity in a nucleus tractus solitarius (NTS) neuron from infant primates exposed to ozone or filtered air (FA). A: schematic drawing showing the brain stem cross section (right), and photograph showing the position of the stimulating electrode in the solitary tract and recording electrode in the NTS (left; bar, 100 μm). Inset: whole cell recording of the NTS neuron at higher magnification (bar, 10 μm). TS, tractus solitarius; X, dorsal motor nucleus of the vagus; XI, hypoglossal nucleus. B: NTS neurons from the ozone-exposed group displayed a reduced responsiveness to synaptic excitation evoked by stimulation of primary afferent fibers in the tractus solitarius (10 successive stimuli) compared with those in the FA-exposed group. C: the same neurons demonstrated an increased spiking in response to depolarizing current injections (18).
COMPLEXITY OF PLASTICITY IN THE NTS

Beyond the proof of concept of the occurrence of plasticity in the NTS (17, 18, 21, 52, 79), NTS neurons appear to have the capacity to undergo complex modes of plasticity observed in other networks. For example, Chen et al. (18) have previously shown that, when infant primates were episodically exposed to ozone over an extended period of time (0.5 ppm, 8 h/day for 5 days every 14 days for 11 episodes), the NTS neurons exhibited a complex plasticity: a decreased tendency to respond to synaptic activation by sensory afferent fibers in the tractus solitarius, which was counterbalanced by an increased nonspecific excitability, as evidenced by a more depolarized resting membrane potential associated with an increased input resistance and an increased spiking response to intracellular injections of depolarizing currents. As shown in Fig. 1B, for the same stimulus intensity applied to the sensory afferent fibers in the tractus solitarius, NTS neurons from the infant primates exposed to ozone were less excitable by synaptic activation compared with the control group. By contrast, the same neurons were more responsive to nonspecific depolarization by injection of depolarizing currents. Figure 1C shows the spiking response to a 50-pA injection in the primate exposed to ozone compared with the control animal. The findings are consistent with a form of homeostatic plasticity in which the strengths of the synaptic inputs are scaled up or down by the concurrent modulation of the responsiveness of the postsynaptic neuron in an attempt to ultimately maintain a stable firing rate of the postsynaptic neurons within a functional range (70). In the example in the Chen study, the enhanced spiking activity might serve to scale up the neuronal responses to a diminished synaptic input from the primary afferent fibers in an attempt to maintain stable signal processing at these proximal synapses in the lung or airway reflex pathways following a prolonged exposure to an altered external environment.

SUMMARY

The NTS is a strategic site in modifying airway reflexes through short-term or long-term plasticity. Given the complexity of synaptic processing of lung- and airway-related sensory input in the NTS, it would not be surprising to see many forms of plasticity with different mechanisms of induction and expression. The challenge is to sort out when and how plasticity occurs and shapes lung and airway reflex function.

Taking advantages of new approaches to study synaptic transmission, site-specific mutagenesis, systems analysis of the neural network, and molecular imaging in conjunction with established methods will further our understanding of airway sensory input and mechanisms of plasticity in the NTS.

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REFERENCES


