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REVIEW

Nodose Ganglia-Modulatory Effects on Respiration

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Summary

The key role of the vagus nerves in the reflex control of breathing is generally accepted. Cardiopulmonary vagal receptors and their afferent connection with the medullary respiratory centers secures the proper regulatory feedback. Section of the vagi at the midcervical level interrupts primary vagal reflexes and those due to activation of lung afferents by neuroactive substances. In this context the present review focuses on the reflex contribution of the inferior (nodose) vagal ganglia to the respiratory pattern, considering that this structure contains perikarya of vagal afferent neurons which house neurotransmitters, neuropeptides and neurochemical substances. In experimental animals with removed sensory input from the lungs (midcervical vagotomy) the following evidence was reported. Transient respiratory suppression in the form of apnoea, occurring after systemic injection of serotonin, adenosine triphosphate and anandamide (N-arachidonoyl-ethanolamine-endogenous cannabinoid neurotransmitter), which was abrogated by nodose ganglionectomy. Preserved nodose-NTS connection conditioned respiratory depression affecting the timing component of the breathing pattern evoked by N-6-cyclopentyl-adenosine (CPA) and inhibition of both respiratory constituents induced by NPY. Stimulatory effect of NPY13-36 on tidal volume required nodosal connection. The cardiovascular effects of majority of the tested substances occurred beyond the nodose ganglia (with exclusion of serotonin and anandamide).

Key words

Vagus nerve • Nodose ganglion • Respiratory pattern • Apnoea • Neurotransmitters

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Introduction

The vagus nerve secures motor and sensory innervation of the airways. Preganglionic motor vagal neurons are localized in the nucleus ambiguous (nA), dorsal vagal nucleus (DVN) and in reticular formation between them in the brainstem (Loewy and Spyer 1990).

Sensory input from nerve endings in the lungs is mediated to vagal afferent neurons in the lower (nodose, NG) and superior (jugular) ganglia. In rats the ganglia are located at distance, the jugular lies intracranially (Zhuo and Helke 1996, Zhuo *et al.* 1997). In the guinea pigs they are close but clearly separated, as smartly illustrated in the paper by Nassenstein *et al.* (2010). Both ganglia have different embryological background. The nodose ganglion is derived from epibranchial placodes and the jugular originates from the neural crest cells, which defines the phenotypes of the vagal fibers (Carr and Undem 2003, Undem *et al.* 2004). The central endings of vagal primary neurons innervating the airways terminate in the nucleus tractus solitarii (NTS) of the medulla oblongata. NTS, NG alike house and releases a variety of neurotransmitters and neuromodulators, which are essential in the regulation of autonomic nervous functions. Primary respiratory vagal reflexes modifying the pattern of breathing, evoked by normal physiological events (lung inflation, activation of chemoreceptors) as well as the effects of chemical substances affecting vagal afferents when injected into the pulmonary circulation,

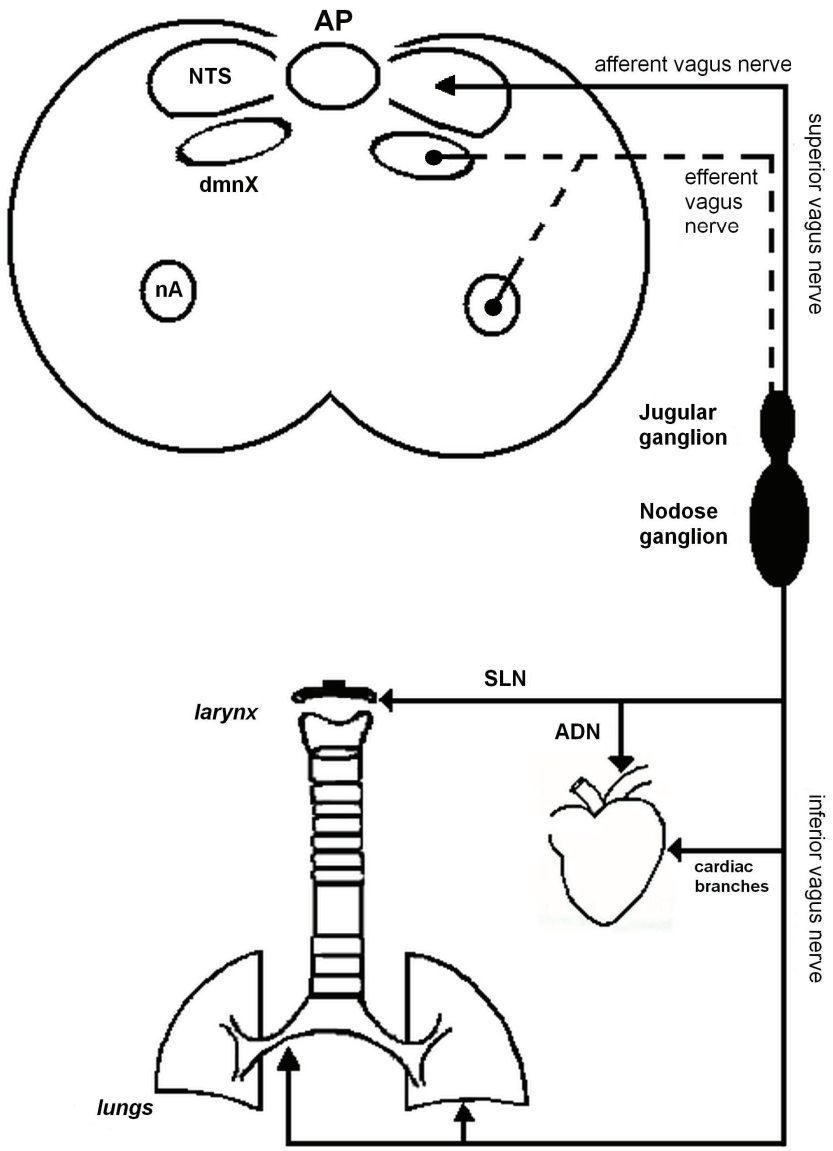

Fig. 1. Schematic drawing of the vagal innervation of the respiratory system and the heart. Abbreviations: AP (area postrema), NTS (nucleus tractus solitarius), dmnX (dorsal motor nucleus of the vagus), nA (nucleus ambiguous), SLN (superior laryngeal nerve), ADN (aortic depressor nerve)

are prevented by midcervical vagotomy. Multiplicity of ionotropic, G-protein coupled or ion channel-gated receptors on vagal sensory afferent fibers activated by various compounds evidenced with the modern techniques (Undem and Carr 2001) indicates that the higher levels of the vagal pathway might be involved in reflex respiratory responses. The present review concentrates on the contribution of the nodosal pathway to the reflex responses to systemic challenge with various neuroactive substances (Fig. 1).

Lung vagal afferents

According to the orthodox, accepted division there are three main types of lung vagal afferent endings: (i) slowly adapting pulmonary stretch receptors (SARs), (ii) rapidly adapting receptors (RARs) both with myelinated fibers and (iii) bronchopulmonary nonmyelinated C-fiber afferents. The two latter respond to mechanical, irritant and chemical stimuli in the airways and produce diverse reflex responses: hyperventilation, augmented breaths, bronchoconstriction, decreases in tidal volume, tachypnoea and cardiovascular effects (Sant'Ambrogio and Widdicombe 2001, Lee and Pisarri 2001). The reflex function of SARs is known since the classical work of Hering and Breuer in 1868. It is considered that summation of SARs activity within the brain stem respiratory groups is acting as a mechanism terminating inspiration, resulting in the decrease in tidal volume and shortening of the inspiratory time (Coleridge and Coleridge 1986, Schelegle and Green 2001).

Albeit this classification is hitherto existing, the

comprehensive research performed in the guinea-pigs, threw a new light on the bronchopulmonary afferent nerves, which belong to above mentioned three categories: C fibers, rapidly adapting stretch receptors, and slowly adapting stretch receptors (Carr and Undem 2003). As addressed in the Introduction the different embryological origin of the vagal nodose and jugular ganglia seems to bring about various functions of the afferent fibers projecting from their somata in the ganglia to the airways. These from the nodose ganglia were in majority rapidly adapting myelinated Aδ, low treshold mechanosensory stretch fibers (RARs and SARs) supplying intrapulmonary airways. Uneven, small quantity of unmyelinated C fibers projected to intrathoracic airways. Afferents arising form the jugular ganglia, Aδ adapting slowly to mechanical stimuli and C fibers, both stimulated by capsaicin, were directed to intrathoracic airways (Riccio *et al.* 1996, Carr and Undem 2003).

Sites and effects of vagotomy

Bilateral midcervical vagotomy prevents the respiratory reflexes conveyed by the vagal afferents generated on its sensory endings. Midcervical division of the vagi in cats, rabbits, dogs and rats induces an increase in tidal volume and slowing down of the breathing rate (Lim *et al.* 1958, Eldridge 1973, Gautier 1973, Paleček and Chválová 1976). The lack of the volume feedback and prolongation of the inspiratory time were reported in dogs, ponies and rabbits following pulmonary vagotomy performed either by hilar stripping of the vagal branches or section of the vagal trunks within the chest (Favier *et al.* 1982, Flynn *et al.* 1985 a, b, Clifford *et al.* 1983, Szereda-Przestaszewska 1986). This neurotomy was evidenced to be effective in eliminating the triad of pulmonary chemoreflex evoked by capsaicin challenge (arrest of breathing, hypotension and bradycardia) in dogs and cats (Toh *et al.* 1955, Coleridge and Coleridge 1984, Clifford *et al.*1987, Haxhiu *et al.* 1988, Kopczyńska and Szereda-Przestaszewska 1998) but not in rats (Kaczyńska and Szereda-Przestaszewska 2000).

Refined, selective sensory vagotomy performed in cats at the level of the nodose ganglia, described first by Mei (1966), has shown that these lung afferents are exclusively involved in the shape of the respiratory pattern while the motor efferents seem to be disregarded (Jammes and Mei 1979).

Neural structure of the nodose ganglia

Extracranial nodose ganglia of the vagus nerve contain somata of the primary vagal afferent neurons predominantly of C and residual of A type fibers (Stansfeld and Wallis 1985). They are pseudounipolar with axon-like process, which bifurcate into the centrally and peripherally directed primary afferent fibers. The peripheral axons compose vagus nerve and its branches and innervate receptors in the respiratory, cardiovascular and gastrointestinal systems. The central axons transmit information from the above mentioned viscera to CNS and terminate in the nucleus of the solitary tract (NTS) in the brainstem (Brodal 1969, Kalia and Mesulam 1980, Donoghue *et al.* 1982 a, b, Puizillout and Gambarelli 1989, Leal-Cardoso *et al.* 1993, Zhuo *et al.* 1997). Supranodosal vagus in the cat was shown to contain about fifty thousands fibers of which scarcely 13 % were myelinated (Mei *et al.* 1980). Likewise, in bronchial branches non-myelinated fibers constituted 90 % of the sensory and motor vagal components (James *et al.* 1982). Separate afferent vagal branches – superior laryngeal (SLN) and aortic depressor nerves (ADN) departure from (enter to) the nodose ganglion usually jointly in rats (Andrew 1954, Sapru and Krieger 1977). Both nerves are composed mainly of the myelinated fibers in cats an rabbits (Agostoni *et al.* 1957, Jordan and Spyer 1978), whereas in rats the proportion of the myelinated fibers accounts for 50 % (SLN) and 20 % for ADN (Hishida *et al.* 1997, Fazan *et al.* 1997).

Neurochemical content of the nodose ganglia

The large body of data obtained from immunohistochemical studies of the nodose ganglia performed in rats detected immunoreactive cells for naturally occurring neuropeptides: substance P, calcitonin-gene related peptide, cholecystokinin, neurokinin A, vasoactive intestinal peptide and somatostatin (Helke and Hill 1988, Balzamo *et al.* 1996). The most extensive and comparable review of Zhuo *et al.* (1997) on the content of neurochemicals within the neurons of the nodose ganglia reveals classic neurotransmitters, neuropeptides and presence of the defined receptors. Therefore this structure appears to serve as an important regulatory mechanism in the cardiovascular and respiratory control.

Chronic supranodose vagotomy has been generally applied in histological studies on the

Table 1. Neurotransmitters, neuropeptides and other neuractive substances that evoke respiratory and/or cardiovascular responses mediated by the intact nodose ganglia.

Substances	Response	References
Serotonin *Phenyldiguanide*	Apnea Bradycardia Hypotension	Jacobs and Comroe (1971)
Serotonin	Apnea	Black *et al.* (1972), Yoshioka *et al.* (1992), Kopczyńska and Szereda-Przestaszewska (2003)
Adenosine triphosphate (ATP)	Apnea	McQueen *et al.* (1998)
Anandamide (AEA)	Apnea Decrease in tidal volume Hypotension	Kopczyńska and Szereda-Przestaszewska (2006)
N 6-cyclopentyl-adenosine (CPA)	Decrease in respiratory rate	Kaczyńska and Szereda-Przestaszewska (2008)
Neuropeptide Y (NPY)	Decrease in tidal volume Decrease in respiratory rate	Kaczyńska and Szereda-Przestaszewska (2010)
NPY 13-36	Increase in tidal volume	Kaczyńska and Szereda-Przestaszewska (2011)

composition and functions of the nerve fibers contained in the vagus nerve (Agostoni *et al.* 1957, Mei *et al.* 1980) and in neurochemical research evidencing neurotransmitters of vagal primary fibers and receptor binding sites within the NTS.

Respiratory impact from the nodose ganglia

Apnoea

There is scarce evidence presented in the earlier reports showing that supranodose connection is essential for the occurrence of respiratory effects in animals with disrupted vagal and/or carotid sinus afferents. This applies to serotonin (5HT), a putative neurotransmitter and phenyldiguanide – $5HT_3$ receptor agonist injected into carotid artery in cats. Respiratory inhibition in the form of apnoea and cardiovascular component: bradycardia and hypotension induced by 5HT injection were not dependent on the integrity of the lung and carotid bodies sensory innervation. This was pioneered by Jacobs and Comroe (1971) and Black *et al.* (1972) who showed that section of the supranodose vagi abolished the apnoea. This respiratory arrest resulted from the direct excitatory effect of 5HT on nodose ganglion cells (Sampson and Jaffe 1974), and was reported before serotonin receptors were described (Peroutka and Snyder 1979). The apnoeic effects of the local injection of 5HT into vascularly isolated nodose ganglion reinforced this site of action (Sutton 1981). Since then it became clear that the majority of vagal afferent neurons are endowed with 5HT receptors (Higashi and Nishi 1982). However, the blockade of two types of 5HT receptors appeared not to be as effective as the transection of the supranodose vagi to abolish post-5HT apnoea induced by systemic challenge in rats and cats (Yoshioka *et al.* 1992, Kopczyńska and Szereda-Przestaszewska 2003). Therefore this body of data indicates that projections issues from the nodose ganglia in midcervically vagotomized animals contribute to the respiratory suppression after challenge with some neurochemical substances endogenous to ganglionic neurons. This relates to the apnoeic effects evoked by stimulation of P_{2X} purinoceptors (receptors for adenosine triphosphate) and endocannabinoid receptors in rats (McQueen *et al.* 1998, Kopczyńska and Szereda-Przestaszewska 2006) (Table 1).

Respiratory depression and stimulation

Respiratory inhibition other than apnoea induced by neurochemicals appears to be less described. Several lines of evidence suggest that adenosine A_1 receptors, endowing the nodosal neurons (Lawrence *et al.* 1997), when activated by systemic challenge with the appropriate agonist (N 6-cyclopentyl-adenosine) caused inhibition of both constituents of the respiratory pattern: tidal volume and respiratory rate in midcervically

vagotomized rats. Supranodose vagotomy prevented the decrease in breathing frequency and showed no effect on the depression of tidal volume. Pretreatment with A_1 receptor antagonist (DPCPX) effectively blocked these respiratory responses. Modulation of frequency and volume was therefore attributed separately to activation of A_1 nodosal and central receptors, respectively (Kaczyńska and Szereda-Przestaszewska 2008).

Neurotransmitters/neuromodulators present in mammalian brain and residing also in the periphery have been seldom tested in experimental animals. Relatively little data are available on respiratory effects of the endogenous non-opioid neuropeptides. It is generally assumed that they induce respiratory depression. Receptors for neuropeptide Y: Y_1 and Y_2 were described to be localized in the nodose ganglia of rabbits, human and rats (Ghilardi *et al.* 1994, McLean *et al.* 1997, Coelho *et al.* 2004). Systemic pretreatment of midcervically vagotomized rats with neuropeptide Y (NPY) was shown to produce bradypnoea with decreased tidal volume. These effects were prevented and reduced by bilateral nodosectomy, respectively. Contrary to NPY, an intravenous injection of NPY13-36, the agonist of Y_2 receptors, evoked respiratory facilitation by stimulating the pattern of breathing in neurally intact rats. The increase in the frequency response appeared to rely on sensory input from the lungs, whereas augmentation in tidal volume was mediated by the supranodose connection.

Intravenous pretreatment with the selective antagonists eliminated the respiratory effects of excitation of Y_1 and Y_2 receptors. These data indicate that NPY induced depressive effects on respiration are mediated *via* nodosal and supranodosal Y_1 receptors feedback, whereas Y_2 enhanced respiratory drive requires modulation of infra and supranodose pathway (Kaczyńska and Szereda-Przestaszewska 2010, 2011).

Extranodosal cardiovascular changes

The cardiovascular alterations resulting from challenge with adenosine agonist (bradycardia and hypotension), NPY (bradycardia and hypertension) and NPY13-36 (invariable HR and hypertension) did not reside in supranodose connection, but appeared to be effectively antagonized by the respective receptors' blockers (Kaczyńska and Szereda-Przestaszewska 2008, 2010, 2011). It is of note that earlier findings inferred the occurrence of cardiovascular effects of 5HT beyond the afferentation from the nodose ganglia in cats (Jacobs and Comroe 1971, Sampson and Jaffe 1974). Subsequent data revealed that lesioned supranodose pathway prevented the hypotensive effects of 5HT in rats and cats (Orer *et al.* 1991, Yoshioka *et al.* 1992, Kopczyńska and Szereda-Przestaszewska 2003).

Mechanism underlying the hypotensive action of adenosine we have tested seems to rely on mediation through the peripheral A_1 receptors expressed in the heart and vasculature (Shryock and Belardinelli 1997, Tabrizchi and Bedi 2001), producing vasodilatation either *via* release of other neurotransmitters (Hedner *et al.* 1982, Stella *et al.* 1993) or modulation from the peripheral A_1 receptors (Schindler *et al.* 2005). Y_1 and Y_2 receptors located on the vascular smooth muscles (Tessel *et al.* 1993, Pedrazzini *et al.* 1998), activated with respective agonists were reported to increase blood pressure (Corder *et al.* 1986, Abrahamsson 2000, Kaczyńska and Szereda-Przestaszewska 2010, 2011). Further experimental data to support these findings are abridged. However, it is important to stress that NPY mimics the cardiovascular effects of catecholamines (van Giersbergen *et al.* 1992).

Limited number of publications dealing with the contribution of the nodose ganglia to regulation of the respiratory reflexes renders an ample consideration perplexing. It is difficult to generalize the evidence provided in this review article. Together, these data suggest that neuroactive substances (adenosine, neuropeptide Y) in inhibiting the respiratory drive do not require sensory input from the lungs. They have a predominant bradypnoeic effect on the timing component of the breathing pattern mediated *via* the supranodose feedback. Evidence to support this concept includes the observation that the coincident inhibition of tidal volume revealed by both substances occurred beyond the supranodosal connection.

It is to be emphasized that in stimulated breathing induced by NPY 13-36, tachypnoea relied on lung vagal pathway, whereas augmentation in tidal volume was attributed to the nodosal connection. It is noteworthy, as formerly mentioned, that the respiratory suppression in the form of apnoea, evoked by activation of serotonin, endocannabinoid and adenosine triphosphate receptors abounded in nodose ganglia requires supranodose feedback.

Conclusions

It was reported earlier that vagotomy or inhibition of axoplasmic transport changes the expression

of neuropeptides in neurones of the nodose ganglia (Zhuo *et al.* 1995) and more recent studies have shown decreased excitability of these neurones after vagotomy (Porreca *et al.* 1999, Lancaster *et al.* 2001). There is no relevant research on such effects of nodosectomy, but it could be inferred from the above evidence that destruction of the supranodosal pathway unsettles transduction from the primary vagal sensory neurones to the binding sites for neurotransmitters within NTS subnuclei and this might variably affect the constituents of the breathing pattern.

Conflict of Interest

There is no conflict of interest.

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