Impact of trigeminal and/or olfactory nerve stimulation on measures of inspiratory neural drive: Implications for breathlessness

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Abstract

The perception of breathlessness is mechanistically linked to the awareness of increased central inspiratory neural drive (IND). Stimulation of upper airway cold receptors on the trigeminal nerve (TGN) with TGN agonists such as menthol or cool air to the face/nose has been hypothesized to reduce breathlessness by decreasing IND. The aim of this systematic scoping review was to identify and summarize the results of studies in animals and humans reporting on the impact of TGN stimulation or blockade on measures of IND. Four databases were searched on January 24th, 2022 and 31 studies were identified, including 19 in laboratory animals and 12 in human participants. Studies in laboratory animals consistently reported that as TGN activity increases, outcomes of IND decrease (e.g., phrenic nerve activity). In humans, stimulation of the TGN with a stream of cool air to the face/nose decreased the sensitivity of the ventilatory chemoreflex response to hypercapnia. This has implications for understanding the neural mechanisms of breathlessness relief with selected TGN agonists.

Key Words

Trigeminal Nerve

Olfactory Nerve

TRPM8 Channels

Nasal Mucosa

Breathlessness

Inspiratory Neural Drive

1. Introduction

The perception of breathlessness is a highly complex process. It is thought to be mechanistically linked, at least in part, to the awareness of increased central inspiratory neural drive (IND, i.e., drive to breathe in) (Banzett, Lansing, & Binks, 2021; Faisal et al., 2016; James et al., 2022). For instance, in healthy adults, increasing IND *via* peripheral chemoreflex stimulation with hypoxia (Moosavi et al., 2003) or central chemoreflex stimulation with hypercapnia (Banzett et al., 1990; Gandevia et al., 1993) causes breathlessness. It follows that any therapeutic intervention capable of decreasing IND has the potential to relieve breathlessness.

In 2000, *Eccles* hypothesized that stimulation of cold receptors on the trigeminal nerve (TGN) with menthol could alleviate breathlessness by decreasing the drive to breathe, alone or in combination with increasing inspiratory airflow or the perception of inspiratory airflow (Eccles, 2000, 2003). The upper airway cold receptors referred to by *Eccles* are most likely the transient receptor potential melastatin-8 (TRPM8) channels located on the TGN. TRPM8 channels, which respond to several specific agonists, such as menthol and cool air (McBride & Whitelaw, 1981; Sloan, De Cort, & Eccles, 1993), elicit sensations of coolness and freshness (Peier et al., 2002). This is in contrast to other TRP channels like TRP Vanilloid-1, which often cause unpleasant stinging and burning sensations when stimulated (Frasnelli, Albrecht, Bryant, & Lundström, 2011). In a placebo-controlled study of healthy men, a menthol lozenge caused a significant increase in voluntary breath-hold time (Sloan et al., 1993), whereas another breath-holding study demonstrated that delivering a stream of cool air to the nose and mouth caused significant

reductions in inspiratory muscle contractions compared to the no airflow control condition (McBride & Whitelaw, 1981). The results of these studies provided indirect support for the hypothesis that activation of TRPM8 channels on the TGN might alleviate breathlessness by decreasing IND. The TGN interacts closely with the olfactory nerve (OFN) to send afferent information from the face and nose to the brain (Brand, 2006); thus, it is possible that the OFN, which can be stimulated by several TGN agonists, including menthol (Renner & Schreiber, 2012), also contributes to the neuromodulation of IND. A recent review on the use of medical aromatherapy in geriatric populations has suggested that stimulating the TGN/OFN with inhaled l-menthol may reduce breathlessness by modifying the perception of inspiratory airflow (Ebihara, Yamasaki, Kozaki, & Ebihara, 2021).

When stimulated, somatosensory information from the TGN travels to the trigeminal ganglion of the cranial nerve and eventually to the trigeminal nuclei in a somatotopic way (Cruyssen & Politis, 2018). These trigeminal nuclei exist in the mesencephalic nucleus (midbrain), principle nucleus (pons), and the spinal nucleus (medulla/upper spinal cord) and represent the trigeminal spinal tract (Cruyssen & Politis, 2018). From there, the somatosensory information travels to the ventral posteromedial nucleus of the thalamus and projects to the postcentral gyrus through the trigeminothalamic tract (Cruyssen & Politis, 2018). Evidence from animal models suggests that stimulation of the TGN in the nasal mucosa results in sensory afferent information also projecting to the nucleus tractus solitarius (Anton & Peppel, 1991), an area of the brain essential to the control of ventilation (Zoccal, Furuya, Bassi, Colombari, & Colombari, 2014).

Several studies have reported that inhalation of l-menthol (an organic compound made synthetically or obtained from peppermint oils (Farco & Grundmann, 2013)) or delivering a flow of cool air to the face and/or nose using a fan (i.e., fan-to-face therapy), which both presumably activate TRPM8 channels on the TGN, alleviates breathlessness at rest and/or during exercise in people with malignant or non-malignant disease (Bausewein, Booth, Gysels, Kühnbach, & Higginson, 2010; Galbraith, Fagan, Perkins, Lynch, & Booth, 2010; Johnson, Booth, Currow, Lam, & Phillips, 2016; Kako et al., 2018; Kanezaki & Ebihara, 2017; Kanezaki, Terada, & Ebihara, 2020, 2021; Long, Cartwright, & Reilly, 2021; Luckett et al., 2017; Marchetti et al., 2015; Nishino, Tagaito, & Sakurai, 1997; Wong, Leong, Chan, Kan, & Cheng, 2017). The mechanism(s) responsible for relief of breathlessness with inhaled l-menthol or fan-to-face therapy are poorly understood, but a companion systematic scoping review from our laboratory has provided evidence that activation of the TGN/OFN with a variety of stimuli, such as menthol and cool airflow to the face/nose, alters the neuronal activity within multiple regions of the human brain implicated in the anticipation and/or perception of breathlessness, including the insular cortex, anterior cingulate cortex, thalamus, and amygdala (Reference from companion scoping review when available). Another possible (complimentary) mechanistic explanation is reduced IND *via* stimulation of the TGN/OFN with l-menthol or fan-to-face therapy.

The aim of this systematic scoping review was therefore to answer the question: *'Does stimulation or inhibition of the TGN/OFN alter indices of IND (e.g., phrenic nerve activity)?'*

2. Methods

This scoping review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension guidelines for scoping reviews (Tricco et al., 2018). Ethics approval was not needed as only published de-identified data were used.

2.1. Information Sources and Search Strategy

Electronic databases, including Ovid MEDLINE, EmBase, PsychInfo and Web of Science, were searched on January 24th, 2022 by a single author (RA) to identify eligible records. The search strategy was drafted by RA in collaboration with a research librarian and finalized by the group of authors. The search strategy for Ovid MEDLINE is presented in **the supplementary material,** and the search terms were modified appropriately for each database.

2.2. Eligibility Criteria

Records were included if they: 1) reported on adult humans or animals; 2) targeted the TGN and/or OFN through either stimulation or inhibition/blockade; 3) examined respiratory outcomes (e.g., post-apneic end-tidal carbon dioxide pressure ($P_{ET}CO_2$), tidal volume (V_T), breathing frequency (f_b), inspiration time (T_I)); and 4) examined phrenic nerve activity or other measures of IND such as activity of inspiratory neurons. Records were excluded if they: 1) explored

conditions irrelevant to our research question such as traumatic brain injury, diaphragm dysfunction or paralysis, and amyotrophic lateral sclerosis; 2) were not a peer-reviewed, primary research study, such as conference abstracts, systematic reviews or meta-analysis, theses, letters to editors, or case studies.

2.3. Selection of Sources of Evidence

All records identified from the electronic search were reviewed by one author (RA) and duplicates were removed. One author (RA) screened remaining unique records for eligibility based on the title and abstract, and then performed full-text review of the of potentially eligible records. For any record that could not be confidently excluded from full-text review, two additional authors were available for consultation (DJ and HL). The reference lists of the included records were screened and any additional citations that met eligibility criteria were included.

2.4. Data Charting Process

A data-charting template was developed *a priori* by a single author (RA) using Microsoft Excel. The template was refined by two other authors (DJ and HL). A single author (RA) independently extracted data from all included studies into the data-charting template. The **supplementary material** contains a summary of the data items that were extracted.

2.5. Synthesis of Results

Study data were reported using the following hierarchical approach. First, it was noted whether animals or human participants were studied, and the specific animal species was recorded. It was then recorded if vagotomy was used in animals. Next, the nerve target(s) were summarized, and it was recorded whether the nerve target(s) was blocked or intact, and what method, if any, was used to stimulate the nerve target(s). Lastly, all respiratory-related outcomes were summarized and dichotomized as either being recorded following stimulation of the trachea or nasal mucosa or measured from either of these areas.

3. Results

3.1. Selection of Sources of Evidence

A total of 264 records were found using the search strategies, with an additional 22 records included through handsearching. After a structured title, abstract, and full text review **(Figure 1),** 31 studies were included. Four of these studies were written in Russian and translated to English by a professional translator.

3.2. Characteristics of Included Studies

Of the 31 included studies, 19 (61%) reported results from animals and 12 (38%) from humans **(Table 1)**. In the animal studies, 8 (25%) targeted the TGN as a whole, whereas 5 (16%) targeted the ethmoidal nerve branch (EN5) of the TGN. Two studies (6%) targeted both the anterior

ethmoidal nerve (AEN) branch and the posterior nasal nerve (PNN) branches of the TGN, whereas another two studies (6%) included the phrenic nerve or the OFN as one of their targets. The following additional nerves were each targeted by individual studies (3%): vagus nerve, hypoglossal nerve, and super laryngeal nerves. One study (3%) targeted the motor trigeminal nucleus (5M) and parabrachial nucleus (PB). Five (16%) of the 19 animal studies employed a complete blockade of either the TGN (n= 4) or the 5M and PB (n= 1).

In the human studies, 4 (13%) used inhaled l-menthol or menthol flavoured chewing gum, 3 (10%) delivered a stream of cool air to the face, and 5 (16%) used a household or hand-held fan pointed to the face.

The interventions used to stimulate the targeted nerves were chemical (29%), thermal (3%), electrical (6%), mechanical (16%), electrical and thermal (9%), mechanical and thermal (9%), hypercapnia (3%), chemical and thermal (3%), mechanical and electrical (3%), and mechanical and chemical (3%) **(Table 1).**

3.3. Effect of TGN blockade on respiratory and IND outcomes in animals

The percentage change in respiratory outcomes during nasal or tracheal breathing following complete TGN blockade with ethyl alcohol in decerebrate cats with intact vagal nerve function is reported in **Figure 2.** After TGN blockade during nasal breathing, minute ventilation (V'_E) increased by 46% ($p<0.001$), tidal volume (V_T) increased by 25% ($p<0.01$), breathing frequency (f_b) increased by 16% ($p<0.01$), total respiratory cycle time (T_{TOT}) decreased by 12% ($p<0.05$),

and expiratory time (T_E) decreased by 16% ($p<0.01$). There was a non-significant decrease in inspiratory time (T_I) by 4% ($p<0.3$). During tracheal breathing, TGN blockade increased V'_E by 6% ($p<0.001$), but otherwise had no significant effect on V_T, f_b, T_{TOT}, T_E and T_I (all $p>0.3$).

The percentage change in respiratory outcomes during nasal or tracheal breathing following TGN blockade in vagotomised and decerebrate cats is reported in **Figure 3.** After TGN blockade during nasal breathing, there was a significant increase of V'_E by 28% ($p<0.01$), but an otherwise non-significant increase in V_T by 19% or f_b by 4.5% (both $p>0.5$). There was a non-significant decrease in T_{TOT}, T_E, and T_I by 0.8%, 2.5%, and 1%, respectively (all $p>0.6$). After TGN blockade during tracheal breathing, the percentage of carbon dioxide ($\%CO_2$) in the alveolar air decreased by 11% ($p<0.01$), the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) decreased by 15.5% ($p<0.001$), V'_E increased by 8-23% ($p<0.001$ to <0.2), V_T increased by 28% ($p<0.02$), and f_b increased by 30% in one study ($p>0.1$) and decreased by 11% another study ($p<0.2$). T_{TOT}, T_E, and T_I increased by 21%, 22%, and 20%, respectively (all $p<0.2$).

3.4. Effect of TGN/OFN stimulation on respiratory and IND outcomes in animals

Twelve studies examined the effect of multiple methods of TGN/OFN stimulation on measures of IND (phrenic nerve activity and respiratory neuron activity) and respiratory outcomes (T_I, V_T, f_b) during nasal or tracheal breathing in various animal species **(Table 1)**. The results of these studies are summarized in **Figure 4.** During nasal breathing, TGN/OFN stimulation was associated with a consistent decrease in phrenic nerve activity, respiratory neuron activity, T_I, V_T

and f_b. Conversely, during tracheal breathing, TGN/OFN stimulation with menthol increased f_b. Nine studies (75%) reported a complete temporary cessation of breathing following TGN/OFN stimulation with a range of stimulants including inhaled ammonia, room temperature water, electrical stimulation, cool air (15°C), menthol, camphor, and eucalyptus. Several of these studies (n=5, 41%) included the EN5 as one of their targets, the branch of the TGN known to elicit the diving reflex.

3.5. Effect of 5M and PB blockade on respiratory and IND outcomes in animals

Figure 5 shows the percentage change in phrenic nerve activity, T_E and T_I following blockade of the 5M and PB compared to no blockade and blockade of the (i) ponticular reticular formation and (ii) facial nerve fiber tract in vagotomised, anesthetized, paralyzed, and mechanically ventilated cats. Blockade of the 5M decreased phrenic nerve activity by ~26% ($p<0.01$), and increased T_E and T_I by 29% and 266%, respectively (both $p<0.05$). Blockade of the PB decreased phrenic nerve activity by 35% ($p<0.01$), and increased T_E and T_I by 42% and 65%, respectively (both $p<0.05$).

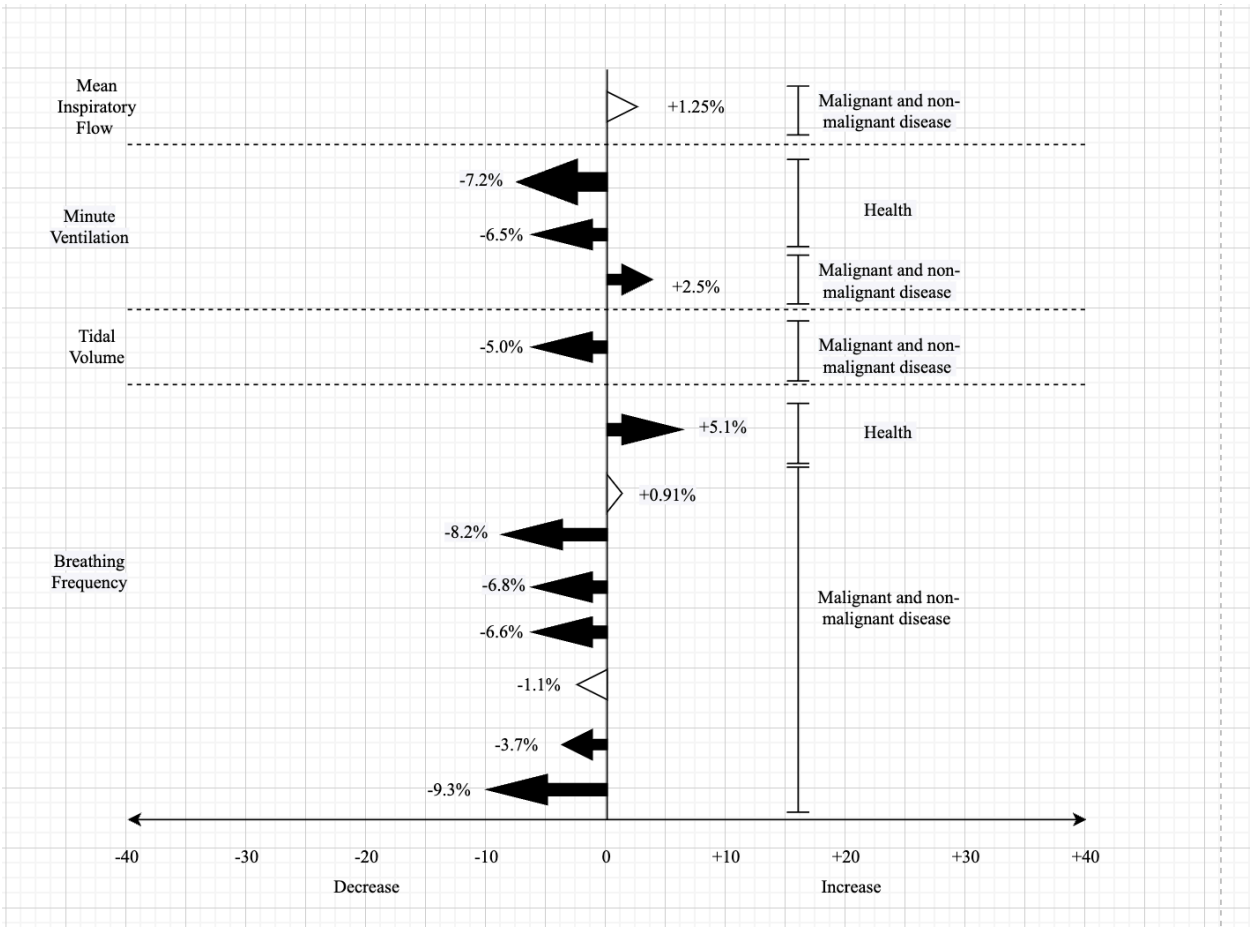
3.6. Effect of TGN/OFN stimulation on respiratory and IND outcomes in humans

The effect of delivering a stream of cool air to the face/nose on ventilatory chemoreflex responses to hypercapnia in healthy humans is summarized in **Figure 6**. Compared to a control condition with no facial airflow, delivering a stream of cool air to the face decreased the ventilatory response to a standardized hypercapnia ($P_{ET}CO_2$ = 55 Torr) by 0.21 $L/min^{-1}/Torr^{-1}$ or

6.5% ($p>0.05$). Compared to delivering a stream of warm air to the face, delivering a stream of cool air to the face decreased the slope (sensitivity) of the ventilatory response to hypercapnia by 0.50 $L/min^{-1}/Torr^{-1}$ (or 16%) and 0.56 $L/min^{-1}/Torr^{-1}$ (or 27%) (both $p<0.05$).

Figure 7 summarizes the effects of delivering a stream of cool air to the face/nose compared to no air, and pointing a fan to the face compared to no fan or a fan pointed to the leg, on respiratory outcomes in human participants. In participants with malignant or non-malignant disease, f_b was decreased by 1.1% - 9.3% with a fan to the face compared to no fan or a fan to the leg, where reductions of f_b greater than 6.6% were deemed significant ($p<0.05$). Otherwise, compared to the respective control or sham condition, a stream of cool air to the face/nose or pointing a fan to the face did not significantly alter V_T/T_I, V'_E, V_T in healthy participants or those with malignant or non-malignant disease ($p>0.05$) (**Figure 7**). Inspiratory reserve volume (IRV) in participants with malignant and non-malignant disease was significantly greater (68.6%; $p<0.05$) with a fan to the face compared to a fan pointed to the leg, perhaps driven by the 5.5% decrease in inspiratory capacity, although this was not significant ($p = 0.06$) (not pictured in Figure 7).

Figure 7. *Effect of delivering a stream of cool air to the face (Burgess & Whitelaw, 1984, 1988; Schwartzstein, Lahive, Pope, Weinberger, & Weiss, 1987) or placing a fan in front of the face (Kako et al., 2018; Kocatepe, Can, & Oruç, 2021; Marchetti et al., 2015; Puspawati, Sitorus, & Herawati, 2017; Wong et al., 2017) on respiratory outcomes in human participants compared to no air/no fan and a fan pointed to the leg.*

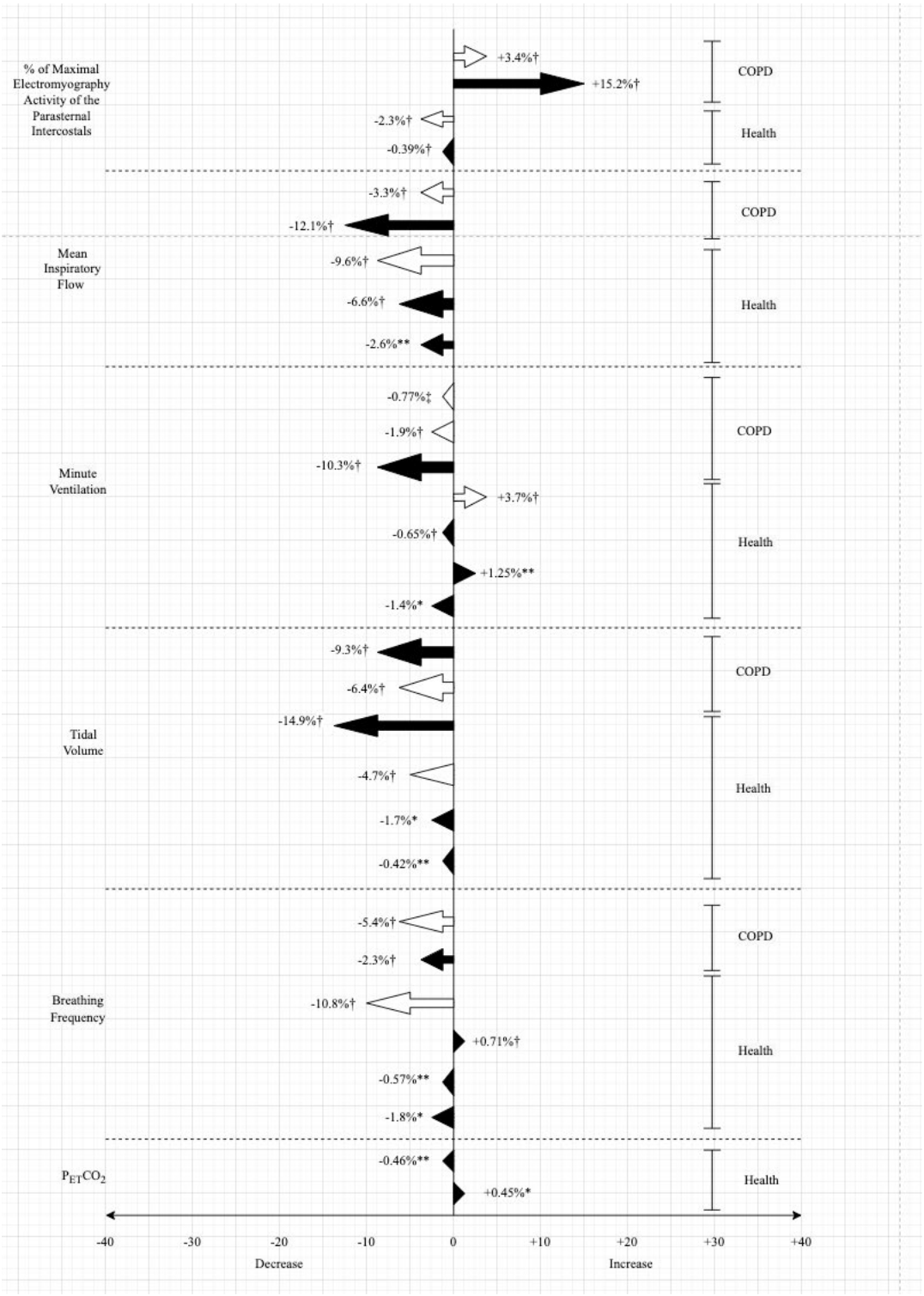


Note: Black arrows depict a stream of cool air to the face or a fan to the face compared to no air or no fan; white arrows depict a stream of cool air to the face or a fan to the face compared to a fan to the leg.

Figure 8 summarizes the effects of inhaled l-menthol or menthol flavoured chewing gum on respiratory outcomes under different breathlessness conditions in human participants. In both healthy participants and people with chronic obstructive pulmonary disease (COPD), there were no significant changes in the percentage of maximal electromyography activity of the parasternal

intercostals ($EMG_{para\%max}$), V_T/T_I, V'_E, V_T, f_b, and $P_{ET}CO_2$ with inhaled l-menthol or menthol-flavoured chewing gum compared to their respective control and sham conditions ($p>0.05$) (**Figure 8**). One study in people with COPD reported that the cognition of inspiratory flow was significantly greater following inhalation of l-menthol compared to no control (~8%) and sham (strawberry scent) (~29%) (both $p<0.05$) (not pictured in Figure 8). Other ventilatory parameters (i.e., T_I, T_E, T_{TOT}, T_I/T_{TOT}, T_E/T_{TOT}, V_T/T_E, $EMG_{para\%max}/V'_E$) were not significantly different in people with COPD or healthy participants following the inhalation of l-menthol or menthol flavoured chewing gum compared to their respective control and sham conditions ($p>0.05$) (not pictured in Figure 8).

Figure 8. *Effects on inhaled l-menthol (Kanezaki & Ebihara, 2017; Kanezaki et al., 2020; Nishino et al., 1997) or menthol flavoured chewing gum (Prieur et al., 2021) on respiratory outcomes compared to control (no scent) or sham (strawberry scent or strawberry flavoured chewing gum) in humans*



Definition of Abbreviations: COPD = chronic obstructive pulmonary disease; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide.

Note: Black arrows depict inhaled l-menthol or menthol flavoured chewing gum compared to control (no scent); white arrows depict inhaled l-menthol compared to sham (strawberry scent). * = breathlessness induced by flow-resistive loading; ** = breathlessness induced by elastic loading; † = breathlessness induced by inspiratory resistive loading; ‡ = breathlessness measured at end-exercise of a 6-minute walk test.

4. Discussion

This systematic scoping review summarized the results of 31 studies published between 1929 and 2022, including 19 mechanistic (reductionist) studies in laboratory animals. The main findings of this review are: (1) in laboratory animals, TGN inhibition was associated with evidence of increased IND, especially during nasal breathing; (2) in laboratory animals, TGN/OFN stimulation was associated with evidence of decreased IND, especially during nasal breathing; (3) in humans, delivering a stream of cool air to the face, which presumably stimulates the TGN, was associated with a decreased central ventilatory chemoreflex response to hypercapnia and; and (4) in humans, inhalation of l-menthol, chewing menthol flavored gum, delivering a stream of cool air to the face, or placing a fan in front of the face, does not consistently alter respiratory outcomes indicative of IND.

Blockade of the TGN in decerebrate cats consistently increased IND both with and without intact vagal nerve input, as evidenced by (1) increased V'_E, V_T, and f_b; and (2) decreased $P_{ET}CO_2$ and $\%CO_2$ in the alveolar air **(Figures 2 and 3)**. In contrast, stimulation of the TGN through various

methods consistently decreased IND, as evidenced by reduced phrenic nerve activity, respiratory neuron activity, T_I, V_T and f_b. TGN stimulation in the nasal mucosa appears to be associated with more consistent and dramatic changes in indices of IND compared to TGN stimulation in the trachea (**Figure 4**). In cats, blockade of the PB (which receives nociceptive, pruritic and thermal information *via* the spinoparabrachial tract from the trigeminal dorsal horn (Chiang et al., 2019)) and of the 5M (which is functionally connected to the trigeminal main sensory nuclei (Slaoui Hasnaoui, Arsenault, Verdier, Obeid, & Kolta, 2020)) served to decrease IND, as evidenced by reduced phrenic nerve activity and increased T_E and T_I (**Figure 5**). The PB and 5M have also been identified as two areas of the brainstem implicated in pontine ventilatory control in animals (Pokorski & Gromysz, 1997). The collective results of these animal studies suggest that TGN afferent input is inversely related to the neuromodulation of IND, particularly when activity of TGN afferents within the nasal mucosa is affected. The apparently greater neuromodulation of IND *via* altered TGN activity during nasal compared to tracheal breathing suggests that upper airway cold receptors (specifically TRPM8 channels), and not receptors found in the lower airways (i.e., trachea), are primarily responsible for modulating afferent TGN information (Eccles, 2000).

Two animal studies wherein menthol was administered directly to the nasal mucosa clearly decreased phrenic nerve activity, T_I and f_b (Perez de Los Cobos Pallares, Bautista, Stanic, Egger, & Dutschmann, 2016; Plevkova et al., 2013). In one of these studies, cool air (10°C) was administered to the nasal mucosa causing a clear reduction in f_b (Plevkova et al., 2013). Conversely, when these authors administered menthol to the trachea, there was a clear increase in f_b (Plevkova et al., 2013). This is in line with previous work in guinea pigs where cooling of

the upper airways significantly decreased V'_E to 85% of control values, mainly driven by the lengthening of T_E by 145% (Orani, Anderson, Sant'Ambrogio, & Sant'Ambrogio, 1991). This was not replicated in warm air trials; however, the addition of l-menthol to warm air prolonged T_E by 1,028% compared to control values (Orani et al., 1991). These responses were (i) substantially reduced following topical anaesthesia of the nasal cavities using a 2% lidocaine solution in the nostrils; and (ii) completely abolished with *laryngeal* anaesthesia using the same 2% lidocaine solution (Orani et al., 1991). This latter finding is contentious to the results from most other studies reviewed herein, which suggest that TGN/OFN afferents from the trachea, and by extension the larynx, do not alter indices of IND and respiratory outcomes as consistently as TGN/OFN afferents from the nasal mucosa.

In humans, delivering a stream of cool air to the face/nose decreased the ventilatory response to hypercapnia by 6.5 - 27% (**Figure 6**) (Burgess & Whitelaw, 1984, 1988; Schwartzstein et al., 1987). Importantly, the ventilatory response to hypercapnia in humans is often used as an index of central chemoreflex sensitivity. Previous research in humans where cool airflow was delivered to the nose inhibited involuntary inspiratory muscle contractions during breath-holding, an effect that disappeared following topical anesthesia of the nose and pharynx with a 10% lidocaine solution (McBride & Whitelaw, 1981). Thus, these findings in humans are congruent with those described in animals, where stimulation of the upper airway cold receptors on the TGN/OFN, and not the lower airways, with selective TRPM8 agonists (i.e., stream of cool air) has an especially notable neuromodulatory effect on IND and the pattern/timing of breathing. However, in humans, delivering a stream of cool air to the face/nose, placing a fan in front of the face, inhaling l-menthol, or chewing menthol flavoured gum, which all presumably stimulate the

TGN/OFN, did not consistently alter respiratory outcomes (e.g., V'_E, V_T, f_b, V_T/T_I) (**Figures 7 and 8**). Clearly, some level of discrepancy exists between measured outcomes from studies in humans and animals, where perhaps IND is not modulated as clearly or consistently in humans. It is possible that the methodological variation of the reviewed studies, specifically the conditions used to provoke breathlessness (e.g., inspiratory resistive loading, elastic loading, exercise), the intervention type and dose (e.g., inhaled l-menthol, menthol flavoured chewing gum, hand-held fans at varying airflow speeds), and the target population (e.g., healthy participants, participants with malignant or non-malignant disease), may have led to the discrepancy in results. Further research using standardized menthol dosages and methods of administration and fan/cool airflow temperature and speeds are recommended to further understand their effect, if any, on ventilatory outcomes in humans.

It is important to recognize the potential role of the mammalian diving reflex on the aforementioned associations between altered TGN/OFN activity and changes of IND. Briefly, the diving reflex is (i) activated by the ethmoidal nerve (EN5, a specific branch of the TGN) when it is completely submerged in water or stimulated with water or saline (McCulloch, Faber, & Panneton, 1999); and (ii) characterized by a pattern of bradycardia, reduced cardiac output with concomitant peripheral vasoconstriction leading to increased mean arterial pressure, and apnea (Dutschmann & Paton, 2002; Panneton & Gan, 2020). Indeed, multiple (n=9) studies included in this review investigated the diving reflex and reported a complete temporary cessation of breathing when the nasal mucosa was stimulated with water (n=3) or when the EN5 was isolated and electrically stimulated (n=5) (Boissonade & Lucier, 1993; Dutschmann &

Herbert, 1996, 1997; Dutschmann & Paton, 2002; J. E. James & De Burgh Daly, 1972) (**Figure 4**).

4.1.Conclusion

The results of this systematic scoping review highlight the existence of an inverse relationship between TGN/OFN activity and indices of IND in laboratory animals and humans; that is, as TGN/OFN activity increases, IND decreases. However, some of the experimental evidence from studies in humans suggested that inhaled l-menthol, menthol flavoured chewing gum, a stream of cool airflow to the face/nose, or a fan directed to the face have less consistent effects on respiratory outcomes, despite convincing reductions in the multiple dimensions of perceived breathlessness, i.e., intensity, unpleasantness, and quality (Kako et al., 2018; Kanezaki & Ebihara, 2017; Kanezaki et al., 2020; Kocatepe et al., 2021; Marchetti et al., 2015; Nishino et al., 1997; Prieur et al., 2021; Puspawati et al., 2017; Wong et al., 2017). Nonetheless, combined with the complimentary review done by our group identifying a similar pattern of brain activation in response to TGN/OFN stimulation compared with anticipation and/or perception of breathlessness (Reference from companion scoping review when available), we have provided a summary of experimental evidence for the potential central neural mechanism(s) underlying relief of breathlessness with administration of TRPM8 agonists in humans, specifically l-menthol or cool airflow to the face **(Figure 9)**. With this evidence, we hypothesize that TGN stimulation with TRPM8 agonists can alleviate breathlessness by (i) decreasing IND, and/or; (ii) altering the neuronal activity of brain regions implicated in the anticipation and/or perception of breathlessness (e.g., insular cortex, amygdala). Most likely, these proposed mechanisms are not

mutually exclusive, but rather (inter)act in concert to help decrease the perception of breathlessness. Previously, it was speculated simply that stimulating upper airway cold receptors (i.e., TRPM8 channels) located on the TGN could relieve breathlessness *via* modulating sensory afferent information traveling to the sensory cortex, thereby 'fooling the brain' into believing the respiratory system is working at a greater capacity than it actually is (Morélot-Panzini, 2017). Our results have gone beyond this speculation and have provided, for the first time, a plausible neurophysiological link between stimulation of the TRPM8 channel on the TGN and potential breathlessness relief. Additional research is warranted to test this hypothesis and, in so doing, improve the management of breathlessness and health status of symptomatic individuals living with a malignant or non-malignant health condition.

Author's Contributions

RA, literature search, study design, data analysis, manuscript preparation. HL, study design, review of the manuscript. ME, AvL, review of the manuscript. DJ, study design, data analysis, review of the manuscript.

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Declaration of Competing Interest

All authors declare they have no conflicting interests.

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Figure 1. *Flow diagram of the literature search*

Figure 2. *Percentage (%) change in respiratory outcomes following trigeminal nerve blockade with ethyl alcohol in decerebrate cats (Glebovskiĭ, 1981)*

Note: white arrows depict nasal breathing; black arrows depict tracheal breathing.

Figure 3. *Percentage (%) change in respiratory outcomes following trigeminal nerve thermal blockade (Glebovskiĭ, Sukhova, & Nazaruk, 1988; Sukhova & Nazaruk, 1990) or trigeminal nerve blockade with absolute ethyl alcohol (Glebovskiĭ & Sukhova, 1983) in vagotomised and decerebrate cats*

Definition of Abbreviations: IND = inspiratory neural drive; $\%CO_2$ = percentage of carbon dioxide; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide.

Note: white arrows depict nasal breathing; black arrows depict tracheal breathing.

Figure 4. *Effect of multiple methods of trigeminal nerve stimulation on measures of inspiratory neural drive and respiratory outcomes during nasal or tracheal breathing in various animal models*

Definition of Abbreviations: TGN = trigeminal nerve; AEN = anterior ethmoidal nerve; PNN = posterior nasal nerve; EN5 = ethmoidal nerve.

Note*:* # = 41 inspiratory neurons located in the nucleus tractus solitarii; ## = 10 neurons demonstrating on-off respiratory activity in the rostral C1 area, including a defined Botzinger neuron. * = studies using methods of stimulation (e.g., ammonia, water submersion, electrical stimulation) to target the diving reflex; ** = studies targeting the ethmoidal nerve (EN5). White arrows depict nasal breathing; black arrows depict tracheal breathing.

Figure 5. *Percentage (%) change in measures of inspiratory neural drive following xylocaine blockade of the motor trigeminal nucleus and medial parabrachial nucleus compared to controls and xylocaine blockade of other structures (ponticular reticular formation and facial nerve fiber tract) in anesthetized, vagotomised, paralyzed, and mechanically ventilated cats (Pokorski & Gromysz, 1997)*

Note: white arrows depict xylocaine blockade of the motor trigeminal nucleus (5M); black arrows depict xylocaine blockade of the medial parabrachial nucleus (PB).

Figure 6. *Effect of delivering a stream of cool air to the face and to the leg on ventilatory chemoreflex responses to CO_2 in healthy humans (Burgess & Whitelaw, 1984, 1988; Schwartzstein et al., 1987)*

Definition of Abbreviations: CO_2 = carbon dioxide; Avg = average; L = liter; min = minute; mmHg= millimeters of mercury; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide.

Note: White arrows depict a stream of cool air to the face compared to control (no airflow); black arrows depict a stream of cool air to the face compared to a stream of warm air to the face.

Figure 7. *Effect of a delivering a stream of cool air to the face (Burgess & Whitelaw, 1984, 1988; Schwartzstein et al., 1987) or placing a fan in front of the face (Kako et al., 2018; Kocatepe et al., 2021; Marchetti et al., 2015; Puspawati et al., 2017; Wong et al., 2017) on respiratory outcomes in human participants compared to no air/no fan and a fan pointed to the leg.*

Note: Black arrows depict a stream of cool air to the face or a fan to the face compared to no air or no fan; white arrows depict a stream of cool air to the face or a fan to the face compared to a fan to the leg.

Figure 8. *Effects on inhaled l-menthol (Kanezaki & Ebihara, 2017; Kanezaki et al., 2020; Nishino et al., 1997) or menthol flavoured chewing gum (Prieur et al., 2021) on respiratory outcomes compared to control (no scent) or sham (strawberry scent or strawberry flavoured chewing gum) in humans*

Definition of Abbreviations: COPD = chronic obstructive pulmonary disease; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide.

Note: Black arrows depict inhaled l-menthol or menthol flavoured chewing gum compared to control (no scent); white arrows depict inhaled l-menthol compared to sham (strawberry scent). * = breathlessness induced by flow-resistive loading; ** = breathlessness induced by elastic loading; † = breathlessness induced by inspiratory resistive loading; ‡ = breathlessness measured at end-exercise of a 6-minute walk test.

Figure 9. *Proposed/working hypothesis on the central neuromodulation of breathlessness in humans with inhaled l-menthol or delivering a stream of cool air to the face*

Table 1. *Characteristics of included studies by publication year*

Author and Year	**n=**	**Species**	**Blockade or Stimulation**	**Nerve Target**	**Type of Stimulus (if applicable)**	**Source of Stimulus/Stimuli**
Allen, 1929	N/A	Rabbits	Stimulation	TGN and OFN	Chemical	Peppermint, menthol, camphor, eucalyptus*
Allen, 1936	N/A	Rabbits, dogs, rats, guinea pigs	Stimulation	TGN and OFN	Chemical	Camphor, eucalyptus, ammonia*
James et al., 1972	N/A	Dogs	Stimulation	EN5 branch of TGN	Thermal	Room temperature water*
Glebosvkii, 1981	19	Cats	Blockade	TGN	N/A	N/A
Glebosvkii et	13	Cats	Blockade	TGN	N/A	N/A

al., 1983						
Burgess et al., 1984	10	Healthy humans	Stimulation	TGN	Thermal	Cold (-4 - 10° Celsius) and warm (23-30° Celsius) air
St John, 1986	19	Cats	Stimulation	TGN, hypoglossal nerve, phrenic nerve	Electrical	Electrical stimulation to brainstem (150-700 μA)
Schwartzstein et al., 1987	30	Healthy humans	Stimulation	TGN	Thermal	Cold air (4-10° Celsius) against right cheek
Burgess et al., 1988	8	Healthy humans	Stimulation	TGN	Thermal	Cold (≈0° Celsius) and warm air (≈32° Celsius)
Glebosvkii et al., 1988	14	Cats	Blockade	TGN	N/A	N/A
Sukhova et al., 1990	7	Cats	Both	TGN	Hypercapnic air	1.1% and 3.7% CO_2
Wallois et al.,	20	Cats	Stimulation	AEN, PNN,	Mechanical	Jets of compressed air and ammonia*

1991				infraorbital nerve	and chemical	
Wallois et al., 1992	18	Cats	Stimulation	AEN, PNN	Electrical and mechanical	Single-shock stimulations (rectangular pulses of 250-500 μs duration: 0.05-2 mA: 0.3-9 V), repetitive stimulation (10-20 Hz for 20-40s), mechanical manual probing of the meati with a thin catheter
Boissonade et al., 1993	16	Cats	Stimulation	Super laryngeal nerve, EN5	Electrical and thermal	Electrical stimulation (10Hz, 0.1-0.2 ms, 0.1-5.0 mA)
Panneton et al., 1995	33	Muskrat (*Ondatra zibethicus)*	Stimulation	TGN	Chemical	Ammonia vapours*
Dutschmann et al., 1996	10	Wistar rats	Stimulation	EN5	Electrical	Electrical stimulation (50 Hz, 50 μs, maximum 5 mA)
Dutschmann	18	Wistar rats	Stimulation	EN5	Electrical and	Electrical stimulation (40 Hz, 50 μs,

et al., 1997					thermal	maximum 5 mA) and room temperature water
Nishino et al., 1997	11	Healthy humans	Stimulation	TGN	Chemical	L-menthol crystal (300 mg) and strawberry-flavored air
Pokorski et al., 1997	20	Cats	Blockade	5M, PB	N/A	N/A
McCulloch et al., 1999	15	Sprague-Dawley rats	Stimulation	TGN	Chemical	Ammonia (100%) vapours
Dutschmann et al., 2002	N/A	Wistar rats	Stimulation	EN5	Electrical and thermal	Electrical stimulation (20 Hz, 10s, 100 μs pulses, 0.5-2 V) and cold saline (100-200 μl, 12-15° Celsius)
Plevkova et al., 2013	N/A	Dunkin Hartley guinea pigs	Stimulation	TGN	Chemical and thermal	Menthol (0.1 mM) and icillin vapours (10 μM, cold air (10° Celsius) and warm air (30° Celsius)
Marchetti et al., 2015	10	Humans with chronic	Stimulation	TGN	Mechanical	Standard house fan with a peak airflow of 840 Ft/min

		obstructive pulmonary disease				
Perez de Los Cobos Pallares et al., 2016	N/A	Sprague Dawley rats	Stimulation	TGN, OFN phrenic nerve, vagus nerve	Chemical	Non-diluted menthol, lavender, rose vapours*
Puspawati et al., 2017	21	Humans with lung cancer	Stimulation	TGN	Mechanical	Hand-held fan with airflow speed at 4 km/h
Wong et al., 2017	30	Humans with terminal cancer	Stimulation	TGN	Mechanical	Hand-held fan with low airflow speed**
Kanezaki et al., 2017	25	Healthy humans	Stimulation	TGN	Chemical	L-menthol scented patch and strawberry scented patch*

Kako et al., 2018	40	Humans with terminal cancer	Stimulation	TGN	Mechanical	Standard household fan with airflow speed to participants' preference**
Kanezaki et al., 2020	43	Healthy humans (n=14) and chronic obstructive pulmonary disease (n=32)	Stimulation	TGN	Chemical	L-menthol scented patch and strawberry scented patch*
Prieur et al., 2021	63	Chronic obstructive pulmonary disease	Stimulation	TGN	Chemical	Menthol flavoured chewing gum (Airwaves Extreme Menthol Extreme, Wrigley)

Kocatepe et al., 2021	96	Humans with lung cancer	Stimulation	TGN	Mechanical	Hand-held fan with an airflow speed of 4 km/h

***Definition of Abbreviations**:* TGN = trigeminal nerve; OFN = olfactory nerve; EN5 = ethmoidal nerve; AEN = anterior ethmoidal nerve; PNN = posterior nasal nerve; 5M = motor trigeminal nucleus; PB = parabrachial nucleus; μA = microampere; CO_2 = carbon dioxide; μs = microseconds; mA = milliampere; V = voltage; Hz = Hertz; s = seconds; ms = milliseconds; mg = milligrams; μl = microliters; mM = millimolar; km = kilometer; h = hour; Ft = feet; m = minute.

*Specific dosage or temperature not given

**Specific speed not given

Supplementary Material

Supplementary Methods

The search strategy used for OVID Medline.

1. exp Trigeminal Nerve/
2. Olfactory Nerve
3. Menthol/ or Cold Temperature/ or TRPM8 channel.mp.
4. Phrenic Nerve/
5. Physical stimulation/ or electrical stimulation/
6. Stimulation, Chemical/
7. Thermal stimulation.mp.
8. Respiration/ or control of breathing.mp.
9. Ventilation.mp. or Pulmonary Ventilation/
10. Breathing pattern.mp.
11. Breathlessness.mp. or Dyspnea/
12. Electromyography/ or neural drive.mp.
13. Efferent Pathways/
14. Impulse.mp.
15. Blockade.mp.
16. Resection.mp.
17. Central nervous system/ or brain/
18. Brain stem/ or trigeminal nuclei/
19. Diving Reflex/
20. Chemoreflex.mp.
21. 1 or 2 or 3 or 4
22. 5 or 6 or 7
23. 8 or 9 or 10 or 11
24. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
25. 21 and 22 and 23 and 24

Supplementary Results

A summary of the data items extracted to summarize the information

Relevant data were extracted from included studies, including:
Study characteristics: title, author(s), year of publication, journal name
Population characteristics: Animal species, humans (y/n)
Nerve characteristics: target nerve(s), diving reflex (y/n), vagotomised (y/n)
Methodology: nerve blockade, neural blockade, intact nerve, stimuli (y/n): stimuli used
Respiratory outcomes: tidal volume, breathing frequency, minute ventilation
Inspiratory neural drive outcomes: PETCO2, total respiratory cycle time, inspiratory time, expiratory time, %CO2 in the alveolar air, phrenic nerve activity, ventilatory response to hypercapnia