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Medullary mediation of the laryngeal adductor reflex: A possible role in sudden infant death syndrome

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ABSTRACT

The laryngeal adductor reflex (LAR) is a laryngeal protective reflex. Vagal afferent polymodal sensory fibres that have cell bodies in the nodose ganglion, originate in the sub-glottal area of the larynx and upper trachea. These polymodal sensory fibres respond to mechanical or chemical stimuli. The central axons of these sensory vagal neurons terminate in the dorsolateral subnuclei of the tractus solitarius in the medulla oblongata. The LAR is a critical, reflex in the pathways that play a protective role in the process of ventilation, and the sychronisation of ventilation with other activities that are undertaken by the oropharyngeal systems including: eating, speaking and singing. Failure of the LAR to operate properly at any time after birth can lead to SIDS, pneumonia or death. Despite the critical nature of this reflex, very little is known about the central pathways and neurotransmitters involved in the management of the LAR and any disorders associated with its failure to act properly.

Here, we review current knowledge concerning the medullary nuclei and neurochemicals involved in the LAR and propose a potential neural pathway that may facilitate future SIDS research.

1. Introduction

The laryngeal adductor reflex (LAR), or glottic closure reflex, is a mechanism that protects the larynx and upper airways from inappropriate inhalation of fluids and other particulate matter. The LAR reflex is evoked by activation of polymodal nociceptors that respond to mechanical or chemical irritation of the laryngeal mucosa, and are important in various laryngeal activities including: coughing, swallowing, sneezing and the laryngeal chemoreflex (LCR). Activation of the LAR prevents foreign matter from entering the lower respiratory tract by closing the glottis and eliciting coughing and swallowing (Altschuler, 2001; Bartlett, 1989). Unfortunately, in susceptible individuals, excessive activation of the LCR can induce fatal apnea because of prolonged glottal closure and laryngospasm. This excessive LCR activation may be a cause of sudden infant death syndrome (SIDS) in susceptible neonates (Leiter and Bohm, 2007; Thach, 2008). However, it remains unknown how the LAR causes SIDS. To better understand potential mechanisms, and develop preventative measures for SIDS, it is essential to understand the central neural circuits of the LAR.

During the LAR, polymodal nociceptors that terminate within the mucosa of the subglottal laryngeal lumen are activated by foreign material. These polymodal nociceptors have cell bodies in the nodose ganglion of the vagus nerve and central axons that terminate in the nucleus of the solitary tract (NTS) (Fig. 1). The peripheral axons of the LAR travel in the superior laryngeal nerve (SLN) (Harding et al., 1978). Electrical stimulation of the central end of the SLN evokes a characteristic reflex of: apnoea, swallowing and rhythmic sympathoexcitation. The sensory inputs from the SLN are processed within the medulla oblongata (Loewy and Burton, 1978; Dutschmann et al., 2014; Wang et al., 2015), pons (Bautista and Dutschmann, 2014; Dutschmann et al., 2004; Miyaoka et al., 1998), and forebrain (Peden and Sweazey, 1999). The medulla oblongata is a critical site for the generation and regulation of respiratory and cardiovascular control, the laryngeal reflex and many other important visceral activities (Bautista et al., 2014; Berkowitz et al., 2005; Calaresu et al., 1975; Farnham and Pilowsky, 2010; Gaede and Pilowsky, 2010; Li et al., 2005; Makeham et al., 2005; Miyawaki et al., 2003; Padley et al., 2003; Pascual-Font et al., 2011;

Abbreviations: AmbL, loose formation of ambiguus nucleus; BötC, Bötzinger complex; FLI, Fos-like immunoreactivity; LCR, laryngeal chemoreflex; LMN, laryngeal motoneurons; NTS, nucleus of the solitary tract; PreBötC, pre-Bötzinger complex; ROb, raphe obscurus nucleus; RVRG, rostral ventral respiratory group; SLN, superior laryngeal nerve; SoLC, SolDL, SolVL, SolV, SoLM, SolIM, SolI, nucleus of the solitary tract, commissural, dorsolateral, ventrolateral, ventral, medial, intermediate and interstitial part; SP5, spinal trigeminal nucleus; TH, tyrosine hydroxylase; VLR, ventrolateral reticular complex; VNC, vestibular nuclear complex.

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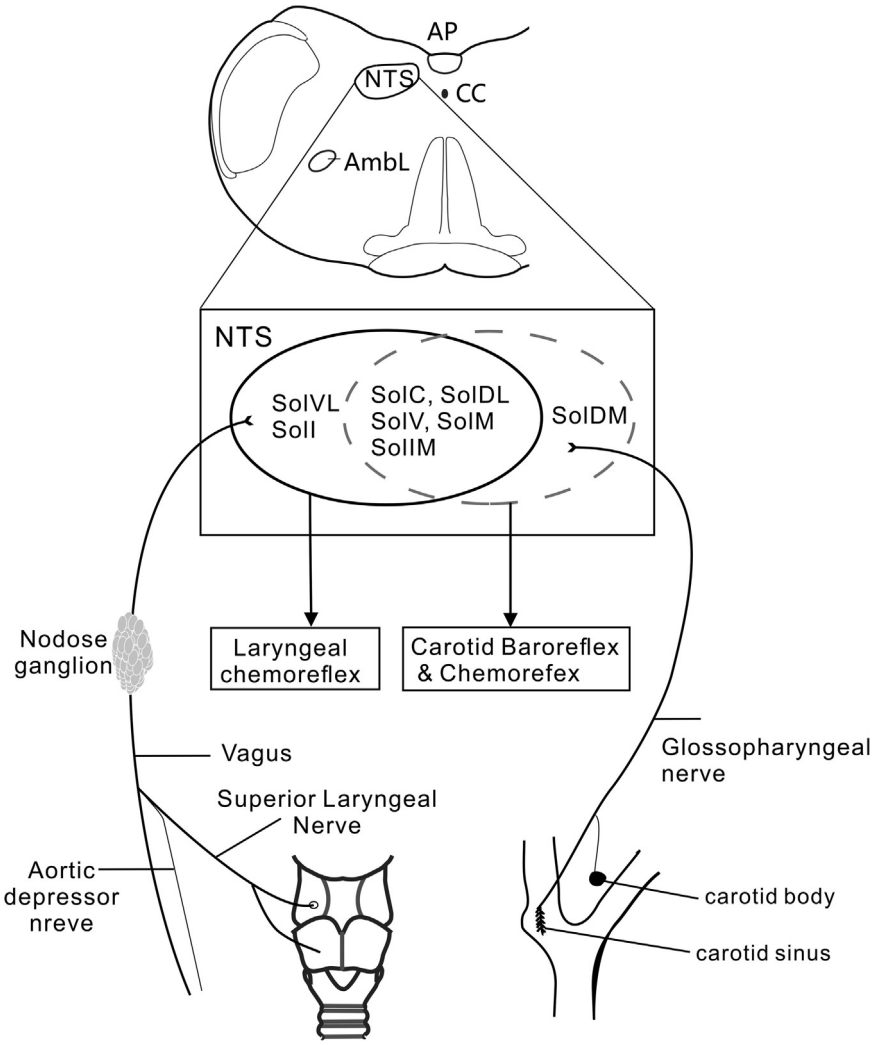

Fig. 1. NTS subnuclei are involved in laryngeal chemoreflex and carotid baroreflex & chemoreflex.
The caudal medullary NTS (enlarged in box) receives afferent inputs from the laryngeal mucosa via the superior laryngeal nerve, or from the carotid body and carotid sinus via the glossopharyngeal nerve, eliciting the laryngeal chemoreflex or the carotid chemo- and baro- reflexes. The ellipse with the solid line contains the NTS sub-nuclei involved in the laryngeal chemoreflex, while the ellipse with the dashed-line contains the NTS sub-nuclei involved in the carotid baro- and chemo-reflexes.
NTS: nucleus of the solitary tract; SolC: commissural subnulei; SolDL: dorsolateral subnuclei; SolVL: ventrolateral subnuclei; SolV: ventral subnuclei; SolM: medial subnuclei; SolIM: intermediate subnuclei; SolI: interstitial subnuclei; SolDM: dorsomedial subnuclei. AP: area postrema; CC: central canal; AmbL: loose formation of nucleus ambiguus.

Pilowsky, 2014; Rahman et al., 2013; Shahid et al., 2012; Spirovski et al., 2012; Springell et al., 2005; Sun et al., 2003; Verner et al., 2004). The medulla oblongata is considered crucial for the LAR. Substantial progress made in this field, includes the finding that during the LAR, different medullary neurotransmitter systems may provide a significant basis for the anatomical understanding of SIDS. Neurotransmitter systems implicated in SIDS on the basis of anatomical location to hypoplastic areas in SIDS victims (Kinney, 2005; Panigrahy et al., 2000), and by virtue of immunohistochemical studies include adrenergic, thyrotropin releasing 'hormone' -ergic, serotonin -ergic, substance P-ergic and midline glutamate and GABA neurons (Murphy et al., 1995; Pilowsky et al., 1997; Sun et al., 1994, 1996, 2002, 2003, 2008, 2011b; Zhao et al., 2015). The complexities of the LAR make it an extremely challenging reflex to understand. On the face of it, glottic closure is the most critical feature, but in addition complex changes in airways pressure, that require careful coordination of almost all respiratory musculature, pharyngeal muscles and total peripheral resistance and heart rate, amongst many others are required. To achieve this, a carefully timed sequence of events takes place within the central nervous system, particularly in the mesencephalon, hindbrain and spinal cord. The net result of this complex series of events is a clearing of any foreign object from the larynx or pharynx, swallowing or spitting, and an appropriate raising or lowering of arterial blood pressure and heart rate.

Laryngeal motoneurons (LMN) located in the loose formation of the nucleus ambiguus (AmbL) (Lobera et al., 1981) receive inputs, and their integrated output can result in glottic closure, causing apnea during the LAR. The medullary regulation of the LAR depends on the interaction of laryngeal motor control and the laryngeal respiratory pathway (Wetmore, 1993).

This review surveys previous studies along with the present work that we have performed and discusses the potential pathway of the LAR by: (1) describing the laryngeal premotor neurons and indicating the possible laryngeal motor roles of these nuclei during the LAR; (2) illustrating the potential internuclear pathways and suggesting the respiratory function of these nuclei during the LAR; (3) elaborating the neurotransmitter system of the LAR and (4) other potential mechanisms of SIDS, and thereby providing suggestions that may facilitate further SIDS research.