Respiratory Physiology & Neurobiology 185 (2013) 203–210

Contents lists available at SciVerse ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Frontiers review

The dorsal motor nucleus of the vagus (DMNV) in sudden infant death syndrome (SIDS): Pathways leading to apoptosis

Charbel Bejjani[a,b], Rita Machaalani[b,c,*], Karen A. Waters[b,c,d]

[a] Sydney Medical Program, University of Sydney, NSW 2006, Australia
[b] Department of Medicine, Room 206, Blackburn Building D06, University of Sydney, NSW 2006, Australia
[c] Bosch Institute, The University of Sydney, NSW 2006, Australia
[d] Children's Hospital, Westmead Sydney, NSW 2145, Australia

ARTICLE INFO

Article history:
Accepted 4 September 2012

Keywords:
Brainstem
Medulla oblongata
Hypoxia
Cell death
Neuropathology
Neurotransmitter

ABSTRACT

Sudden infant death syndrome (SIDS) remains the commonest cause of death in the post-neonatal period in the developed world. A leading hypothesis is that an abnormality in the brainstem of infants who succumb to SIDS, either causes or predisposes to failure to respond appropriately to an exogenous stressor. Neuronal apoptosis can lead to loss of cardiorespiratory reflexes, compromise of the infant's ability to respond to stressors such as hypoxia, and ultimately a sleep-related death. The dorsal motor nucleus of the vagus (DMNV) is a medullary autonomic nucleus where abnormalities have regularly been identified in SIDS research. This review collates neurochemical findings documented over the last 30 years, including data from our laboratory focusing on neuronal apoptosis and the DMNV, and provides potential therapeutic interventions targeting neurotransmitters, growth factors and/or genes.

1. Introduction

SIDS is defined as the sudden sleep-related death of an infant in the post-neonatal period (1–12 months) that remains unexplained after a complete autopsy, death scene investigation and review of clinical history (Krous et al., 2004). In developed countries, SIDS is currently the most common single cause of death in the post-neonatal period (Kinney, 2009). Although the actual cause of death remains unknown, SIDS is associated with a number of risk factors, including male gender, smoke exposure and prone sleeping (Byard and Krous, 2004). The leading hypothesis is that the brainstem of SIDS infants is abnormally developed, leading to the loss of cardiorespiratory, arousal and autonomic reflexes in the face of homeostatic stressors, such as hypoxia, ultimately leading to a sleep-related death (Kinney, 2009). Neuropathological studies of the SIDS brainstem provide insights into mechanisms that might underlie SIDS.

2. Sudden infant death syndrome (SIDS): risk factors and the brainstem hypothesis

Many pre- and post-natal epidemiological risk factors have been identified for SIDS, including prone-sleeping position, post-neonatal apnoea, smoke exposure, bed sharing, premature birth/low birth-weight, family history of SIDS and ethnicity (being aboriginal) (Moon et al., 2007). Three main lines of evidence that support brainstem pathology as the primary cause of SIDS were recently reviewed (Kinney, 2009). In summary, they include: (1) established human and animal data that the brainstem is a major site responsible for the control of respiration and autonomic regulation; (2) prospective studies that show SIDS infants displayed prior subclinical defects in cardiorespiratory and arousal control consistent with brainstem dysfunction, and (3) pathological evidence of abnormalities in SIDS brainstems, particularly regarding the expression of neurotransmitter and receptor systems (reviewed in Kinney, 2009), and markers of cell death (apoptosis) (Sparks and Hunsaker, 2002), within the medulla oblongata. Regarding point (2) above, one of the defects observed by Kahn et al. (1992) was more frequent occurrence of obstructive apnoeas in the infants studied prior to their death from SIDS.

Abbreviations: 5HT, 5-hydroxytryptamine or serotonin; $5HT_{1A}R$, serotonin receptor sub-type 1A; $5HT_{2A}R$, serotonin receptor sub-type 2A; 5HTT, serotonin transporter protein; ACh, acetylcholine; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium cation; ChAT, choline acetyltransferase; DA, dopamine; DMNV, dorsal motor nucleus of the vagus; IHC, immunohistochemistry; IHH, intermittent hypercapnic hypoxia; K^+, potassium cation; nAChR, nicotinic acetylcholine receptor; Na^+, sodium cation; NMDA, N-Methyl-D-aspartate; NR1, N-Methyl-D-aspartate receptor subunit-1; SIDS, sudden infant death syndrome; TH, tyrosine hydroxylase; TrkB, tyrosine kinase receptor B; TUNEL, d**U**TP-digoxigenin **n**ick-**e**nd **l**abelling.

* Corresponding author at: Department of Medicine, Room 206, Blackburn Building D06, University of Sydney, NSW 2006, Australia. Tel.: +61 2 9351 3851; fax: +61 2 9550 3851.
E-mail addresses: rita.machaalani@sydney.edu.au, ritam@med.usyd.edu.au (R. Machaalani).

1569-9048/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.resp.2012.09.001

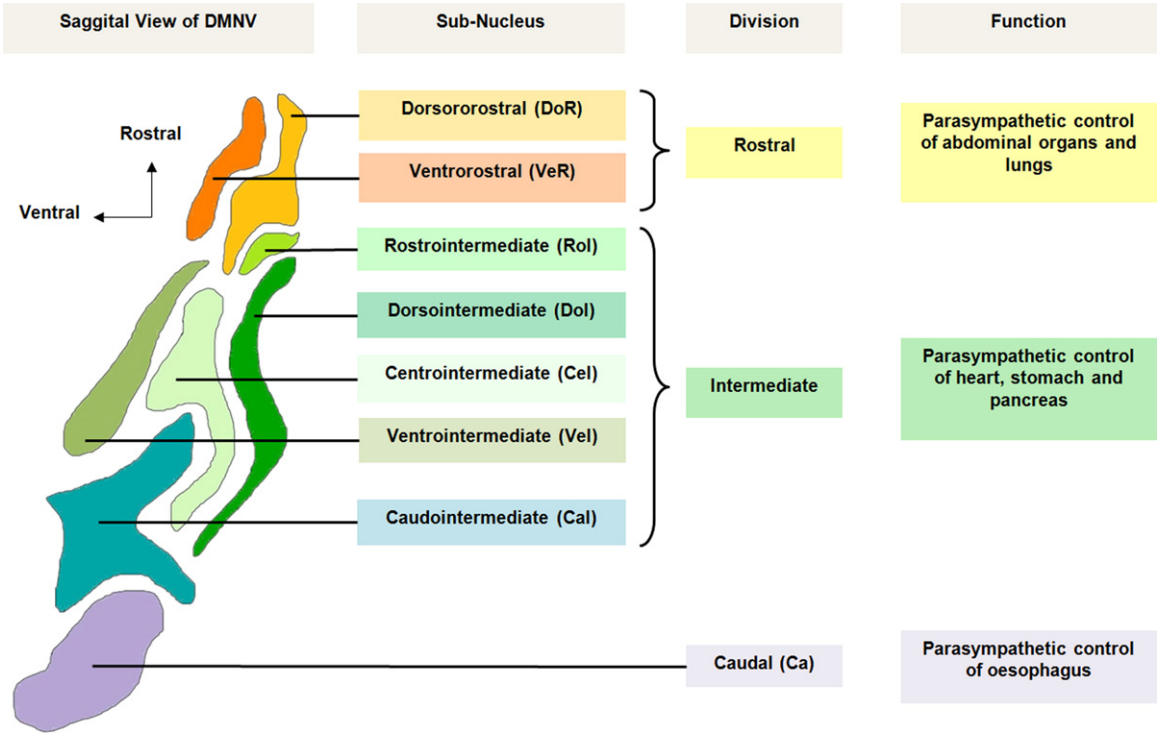

Fig. 1. Saggital dissection of the DMNV correlating data between Huang et al. (1993) and Getz and Sirnes (1949). Note that the top of the diagram correlates with the rostral medulla (superior), while the left of the diagram correlates with the ventral (anterior). The rostral division is divided into two sub-nuclei, the intermediate division is divided into five sub-nuclei while the caudal division remained undivided. Functionally, the DMNV was responsible for parasympathetic output; the rostral division was responsible for control of some abdominal organs and lungs, the intermediate division was responsible for control of heart, stomach and pancreas while the caudal division was responsible for control of oesophagus.

Intermittent hypoxia is postulated to cause downstream central nervous system (CNS) effects, including brainstem abnormalities that predispose infants to SIDS (perhaps underlying their vulnerability). Recent evidence from 17 healthy term infants strongly suggests a relationship between prone sleeping and cerebral deoxygenation (Wong et al., 2011). Evidence from animal models suggests that repetitive exposure to hypoxia causes a progressive blunting of arousal (Waters and Tinworth, 2005) and autonomic responses (e.g. heart rate) (Darnall et al., 2010). Whereas intermittent hypoxia has attracted copious amounts of research, most studies of hypercapnia relate to the changes in clinically detectable ventilatory responses rather than biochemical or microscopic (neuropathological) changes (Anwar et al., 1993; Coleman et al., 1987; Smith et al., 2010). As a result, little information is available regarding pathological consequences of hypercapnia on the infant brain. However, repetitive hypercapnia in conjunction with hypoxia may well be involved in the pathophysiology of SIDS, as it likely occurs in modifiable risk factors that include prone sleeping and obstructive apnoeas. This position has been pursued by our laboratory through our studies with piglets exposed to intermittent hypercapnic hypoxia (IHH), and has yielded neuropathological results that mirror those of SIDS infants.

3. The dorsal motor nucleus of the vagus (DMNV)

The DMNV is located in the dorsomedial aspect of the medulla oblongata of the brainstem. The functionality of the DMNV is region dependent; Huang et al. (1993) sub-divided the human DMNV into rostral, intermediate, and caudal divisions, and into several sub-nuclei based on differences in neuronal morphology, density and acetyl cholinesterase activity. Functionally, the DMNV contributes to the efferent parasympathetic function of the vagus nerve (Siegel and Sapru, 2006). An experiment on seven rabbits by Getz and Sirnes (1949) suggested a somatotopic localisation of function within the DMNV. The rostral division was reported to be responsible for the parasympathetic innervation of abdominal organs and the lungs (Getz and Sirnes, 1949); a finding confirmed by Katz and Karten (1985) in the pigeon. The intermediate division innervated the stomach (Katz and Karten, 1985; Okumura and Namiki, 1990; Siaud et al., 1990), heart (Ellenberger et al., 1983; Getz and Sirnes, 1949; Jordan et al., 1982) and pancreas (Weaver, 1980). There was evidence to suggest that the caudal division was responsible for control of oesophageal function (Getz and Sirnes, 1949; Katz and Karten, 1985). Fig. 1 is a schematic cohesion of the structural and functional data identified to date.

The role of the DMNV in respiratory regulation can be considered from several aspects. The DMNV preganglionic parasympathetic stroma send fibres to various thoracoabdominal viscera through the vagus nerve, in turn causing bronchoconstriction via muscarinic type 3 (M3) receptors in the lungs (Jordan, 2001). In animal models, stimuli that enhance inspiration tend to cause bronchoconstriction while those that stimulate expiration tended to dilate (Jordan, 2001). This phenomenon is in vivo evidence of the neuronal anatomic relationship between various brainstem nuclei demonstrated by Zec and Kinney (2003). The potential therefore exists for other (currently unknown) relationships with important implications in the pathophysiology of SIDS.

The DMNV regulates part of the parasympathetic output to the heart, via the vagus nerve. Vagal output causes a decrease in heart rate in response to increased blood pressure via excitation of peripheral baroreceptors alone (Okada and Miura, 1997). Additionally, cardiac vagal tone is inhibited during the inspiratory phase of respiration, thought to be mediated by medullary inspiratory neurons, causing an increase in heart rate (Dampney, 1994). Furthermore, Talman et al. (1992) demonstrated that by inhibiting preganglionic neurons in the DMNV in rats, one can elicit an