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The physiological determinants of Sudden Infant Death Syndrome "

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Abstract

It is well-established that environmental and biological risk factors contribute to Sudden Infant Death Syndrome (SIDS). There is also growing consensus that SIDS requires the intersection of multiple risk factors that result in the failure of an infant to overcome cardio-respiratory challenges. Thus, the critical next steps in understanding SIDS are to unravel the physiological determinants that actually cause the sudden death, to synthesize how these determinants are affected by the known risk factors, and to develop novel ideas for SIDS prevention. In this review, we will examine current and emerging perspectives related to cardio-respiratory dysfunctions in SIDS. Specifically, we will review: (1) the role of the preBötzinger complex (preBötC) as a multi-functional network that is critically involved in the failure to adequately respond to hypoxic and hypercapnic challenges; (2) the potential involvement of the pre-BötC in the gender and age distributions that are characteristic for SIDS; (3) the link between SIDS and prematurity; and (4) the potential relationship between SIDS, auditory function, and central chemosensitivity. Each section underscores the importance of marrying the epidemiological and pathological data to experimental data in order to understand the physiological determinants of this syndrome. We hope that a better understanding will lead to novel ways to reduce the risk to succumb to SIDS.

Keywords

Sudden Infant Death Syndrome; Hypoxia; Arousal; Gasping; Sigh; Gender

1. Introduction

Sudden Infant Death Syndrome (SIDS) is the unexpected death of an infant less than twelve months of age that cannot be explained after thorough investigation, death scene examination, and review of clinical history (CDC, 2012). While the precise cause of death is unknown, it is well-established that SIDS correlates with infant sleep position and deficiencies in cardio-respiratory function. The intense efforts to better understand the etiology of SIDS has led to the development of a triple risk model involving (1) a vulnerable infant; (2) a critical period of development in homeostatic control; and (3) an exogenous

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stressor (Filiano and Kinney, 1994). According to this generalized model, the intersection of these risk factors leads to a significant increase in the chance of SIDS. While two of the three risk factors are intimately related to the biology of the infant, the third factor, an exogenous stressor, recognizes the important role environment plays in the pathogenesis of the syndrome. Perhaps the most recognized exogenous stressor correlating to SIDS is an infant sleeping in the prone position. In 1996, the United States launched the Back-to-Sleep campaign to better educate the public about the potential danger of infants sleeping in the prone position. This campaign dramatically reduced the occurrence of SIDS (Mage and Donner, 2009; Trachtenberg et al., 2012). However, despite the success of this campaign, SIDS remains a leading cause of infant death (CDC, 2012). Furthermore, a recent report by Trachtenberg et al. (2012) finds that although the relative contributions of risk factors for SIDS have changed, the majority of SIDS cases still involve both, intrinsic and extrinsic risk factors (Trachtenberg et al., 2012).

1.1. The prone sleeping position: an exogenous stressor of respiratory physiology in SIDS

In 1985, Davies described the exceedingly rare occurrence of cot death (i.e., SIDS) within the Hong Kong population when compared to the occurrence in western countries, and while several possible reasons were proposed for this difference, Davies recognized the potential that infant sleep position may have in SIDS (Davies, 1985). Subsequent reports found epidemiological and clinical evidence to support that the prone sleeping position correlates with increased risk of SIDS (de Jonge et al., 1989; McGlashan, 1989; Chiodini and Thach, 1993; Kemp et al., 1993; Trachtenberg et al., 2012).

As an exogenous stressor of SIDS, a wide variety of events may occur leading to infant death when in the prone sleeping position. These events range from thermal stress (Fleming et al., 1993), to airway compression or collapse (Krous et al., 2008; Becher et al., 2012), to re-breathing of exhaled gases (Chiodini and Thach, 1993). However, a common intersection among these events appears to be the occurrence of a catastrophic life-threatening event involving cardio-respiratory distress that the SIDS victim does not successfully overcome.

It is important, however, to recognize that while the prone sleeping position is a risk factor, alone, it does not cause SIDS. SIDS occurs only when environmental challenges (i.e., extrinsic risk factors) and intrinsic risk factors intersect (Lewak, 2012). Thus, while the prone sleeping position may set the stage for SIDS, only vulnerable infants succumb to SIDS. To explore potential physiological vulnerabilities in SIDS, this review will focus on four issues derived from clinical observations and emerging perspectives from experimental models. Specifically, we will look at: (1) insights gained from studying the preBötC, an area critical for the generation of different forms of breathing; (2) gender and age distribution of SIDS etiology; (3) the persistent link between SIDS and prematurity; and (4) the intersection of SIDS, central chemosensitivity, and auditory function.

2. SIDS and central cardio-respiratory control

2.1. Sighs, gasps, and the arousal response

Recognition that the prone position is a major SIDS risk factor has not only saved lives through the Back-to-Sleep campaign but also provides critical mechanistic insights into the physiological determinants of SIDS. The insights gained are consistent with a final common pathway of cardio-respiratory distress that SIDS victims experience involving arousal and/or auto-resuscitation deficiencies. Specifically, an infant sleeping in the face-down position re-breathes exhaled gases which leads to a build-up of inspired CO₂ with a concomitant decrease in inspired O₂ (Kemp and Thach, 1991; Bolton et al., 1993; Chiodini and Thach, 1993; Kemp et al., 1993). Under normal conditions increased CO₂ (i.e., hypercapnia) is a physiological stimulus that leads to a stereotypical arousal response that relieves the build-

up of end-tidal CO₂ and refreshes the inspired O₂ supply of the infant (Lijowska et al., 1997; McNamara et al., 1998; Ayas et al., 2000; Thach, 2002; Masa et al., 2003; Parslow et al., 2003; Fewell, 2005; Horne et al., 2005). This arousal response constitutes a powerful mechanism that normally protects an infant from respiratory distress associated with the prone position (Fig. 1). However, prospective studies have shown that spontaneous and induced arousals during sleep are decreased in SIDS victims indicating an innate susceptibility was present before the final event (McCulloch et al., 1982; Dunne et al., 1992; Kahn et al., 1992; Schechtman et al., 1992; Sawaguchi et al., 2005; Kato et al., 2006). Thus, any factor that blunts the initiation or effectiveness of the arousal response may increase the risk for SIDS (Franco et al., 2010).

In the case of the prone position, the stimuli evoking arousal are specifically increased CO₂ and/or decreased O₂ (Berry and Gleeson, 1997), but the same stereotypical pattern of arousal can be activated spontaneously or triggered by other sensory stimuli (Thach and Lijowska, 1996; McNamara et al., 1998). In all cases, infant arousal begins with the occurrence of a sigh (i.e., augmented breath), followed by thrashing, eye opening, and repositioning of the head which ultimately ameliorates the hypercapnic/hypoxic challenge experienced by a sleeping infant (Lijowska et al., 1997; McNamara et al., 1998). Thus, the sigh appears to be an event initiating both subcortical and cortical arousals (Lijowska et al., 1997; McNamara et al., 1998). In this context, the sigh can be considered as a central nervous system adaptation that responds to changes in blood gases and initiates a series of events that lead to arousal. Indeed, the generation of the sigh is very sensitive to hypoxic challenges (Cherniack et al., 1981; Bell and Haouzi, 2009, 2010). Moreover, the very network that is responsible for the generation of the sigh, the preBötC, is intrinsically sensitive to hypoxia and facilitates the generation of sighs (Lieske et al., 2000; Telgkamp et al., 2002; Tryba et al., 2008; Hill et al., 2011).

Interestingly, in addition to its role in arousal, the sigh also has a significant role in maintaining baseline blood O₂ levels and preventing atelectasis (Hoch et al., 1998; Hess and Bigatello, 2002; Cammarota et al., 2011). Spontaneous sighs are very frequent in the first hours after birth, when the likelihood of atelectasis is high, and gradually fall over the next few days and months (Fleming et al., 1984). Especially during nonREM sleep, the sigh is succeeded by a post-sigh apnea and prominently exhibits respiratory sinus arrhythmia, a form of cardio-respiratory coupling indicative of parasympathetic tone (Fleming et al., 1984; Thach and Lijowska, 1996; Hoch et al., 1998). While this sigh-coupled heart rate response may be important for coordinating cardio-respiratory function, it also correlates with degree of cortical arousal (Thach and Lijowska, 1996; Thach, 2002). Although not all studies report a difference in sigh generation (Kahn et al., 1992; Franco et al., 1998; Kato et al., 2001), there is evidence indicating that a significant number of SIDS victims exhibit fewer sighs (Kahn et al., 1988) as well as lower heart rate variability during a sigh (Franco et al., 2003). The failure to produce effective sighs decreases the likelihood of arousal and may increase the risk of SIDS. Inadequate arousal will exaggerate a normally mild respiratory challenge into a potentially catastrophic form of respiratory distress by perpetuating a state of severe hypoxia and bradycardia.

During a prolonged hypoxic challenge, i.e., when sighs fail to arouse the infant or if it is impossible for the infant to escape the re-breathing condition, breathing stereotypically transitions from a state of eupnea to gasping (Fig. 1, (Hunt, 1992; Poets et al., 1999; Harper et al., 2000)). Gasping is characterized by periodic short breaths with fast rise and fall times (Cherniack et al., 1971; Richter et al., 1991; Hunt, 1992; Poets et al., 1999; Harper et al., 2000; Pena and Aguilera, 2007), and, similar to sighs, gasping produces changes in heart rate (Hunt, 1992; Poets et al., 1999; Harper et al., 2000). The gasping behavior can be considered a mechanism of last resort capable of inducing auto-resuscitation during a

hypoxic challenge (Hunt, 1992; Poets et al., 1999; Harper et al., 2000). As with sigh generation, the preBötC, which is intrinsically sensitive to hypoxia, generates the gasping rhythm (Pena et al., 2004; Tryba et al., 2006; Viemari et al., 2011; Quintana et al., 2012). Unfortunately, in SIDS victims, gasping appears to be ineffective at increasing heart rate and gasps are generated for only a short period of time during severe hypoxia (Poets et al., 1999). These differences likely impair the efficacy of a gasp to increase blood oxygen levels, trigger auto-resuscitation, and increase the chance of survival. At any point, environmental factors may interact and augment these physiological vulnerabilities. For instance, high ambient temperatures have been shown to decrease basal oxygen saturation, increase arousal thresholds, and decrease gasping in infants (Serdarevich and Fewell, 1999; Franco et al., 2000, 2001). Thus, extrinsic environmental factors may exaggerate innate physiological vulnerabilities to increase SIDS risk.

As stated above, the hypoxic ventilatory response is characterized by eupneic augmentation and sigh generation followed by a state of gasping (Hunt, 1992; Poets et al., 1999; Harper et al., 2000). Impaired arousal and autoresuscitation during these periods are generally the focus of SIDS research. However, a third and potentially critical, yet often overlooked phase of respiratory vulnerability occurs upon reoxygenation. During reoxygenation, a silent period termed the post-hypoxic ventilatory depression creates a transition between gasping and eupnea (Lieske et al., 2000; Hill et al., 2011; Garcia et al., 2013a). Any impairment that increases the length of the post-hypoxic ventilatory depression or otherwise impairs the reestablishment of eupnea may contribute to SIDS. This may be especially true when early resuscitation efforts fail during SIDS events. In the next section, the physiological underpinnings of eupnea, sigh, and gasp generation will be discussed in conjunction with central oxygen sensitivity and network reconfiguration during hypoxia (Lieske et al., 2000; Pena et al., 2004; Hill et al., 2011).

2.2. The concept of network reconfiguration is critical for understanding SIDS

One of the biggest puzzles in understanding SIDS is why children that succumb to SIDS appear to breath normally under control conditions (Kahn et al., 1988), yet fail to adequately sigh, gasp, autoresuscitate, and arouse during an environmental challenge. What we need to understand are the mechanisms that differentiate gasping and sighing from those of normal breathing. Without understanding these differences, we will be unable to identify vulnerable infants before it is too late. For this reason, this section is dedicated to the mechanisms that underlie the generation of breathing, gasping, and sighing. In the brainstem, central neural networks integrate sensory inputs, generate respiratory rhythms, and produce coordinated motor output in order to control the timing, amplitude, and duration of each breath. This is true for eupnea, sigh, and gasping behaviors although initially sighs and gasps were thought to be simple reflexes (Bartlett, 1971; Wulbrand et al., 2008). Breathing behavior emerges through the integration of several neural populations within the ventral respiratory column including the preBötzinger complex (preBötC), Bötzing complex, Retrotrapezoid Nucleus/Parafacial respiratory group, and also the Kölliker-Fuse as well as some cortical and cerebellar networks (Ramirez et al., 2012). A popular view was that different types of breathing activities were produced by separate and distinct centers. Many believed that a so-called pneumotaxic center exists in the pons while a gasping center was thought to be located in the ventrolateral medulla (Lumsden, 1923; Fung and St John, 1994; St John, 1996; St-John et al., 2009). This view was based on simple lesion experiments. To the authors undertaking these studies, the medulla, and in particular the preBötC was thought to be the center for gasping and not eupneic breathing. Consequently, pathological changes associated with SIDS in this hypothesized gasping center would provide important insights only into failed autoresuscitation (Mansouri et al., 2001).

This hypothesis was challenged by Ramirez et al. (1998) who first demonstrated in *in vivo* cats that eupnea, i.e., normal breathing, ceases upon lesioning of the preBötC within the ventrolateral medulla (Ramirez et al., 1998). The introduction of modern genetic tools provided even stronger support that the preBötC is essential for eupneic breathing (McKay et al., 2005; Tan et al., 2008; Bouvier et al., 2010; Gray et al., 2010; Tan et al., 2010). Moreover, the concept that separate centers generate different forms of breathing was challenged by a much more plastic concept, i.e., that different forms of breathing are generated by network reconfiguration (Lieske et al., 2000). Specifically, this concept proposes that the same network can generate more than one breathing pattern by undergoing a network reconfiguration (Lieske et al., 2000). The study by Lieske et al. (2000) demonstrated that the preBötC, even when isolated in a brainstem slice, is capable of producing neural rhythms fundamental to the generation of three significantly different respiratory activities: eupnea, sighs, and gasps ((Lieske et al., 2000) Fig. 2A).

The concept of network reconfiguration was a significant conceptual departure from the contemporary understanding of its time, and as discussed in this review, the implications of this conceptual change are important to understanding the physiological determinants of SIDS. One of the ramifications is that a pathological change discovered in the preBötC does not automatically suggest that this pathology relates to gasping as any pathology in the preBötC could also affect eupnea and sighing. Thus, a thorough physiological understanding of the preBötC is essential to explain how a hypoxic challenge could affect gasping and sighing but not normal breathing.

2.3. The different network states of the preBötC and their relevance for SIDS

The preBötC is a bilateral network located in the ventral lateral medulla and is composed of a heterogeneous population of neurons (for a comprehensive review see (Ramirez et al., 2012)). This heterogeneous population can be classified into three types based on their intrinsic discharge properties: non-pacemaker neurons, persistent sodium current dependent (bursting) pacemaker neurons (PM_{INaP}), and non-specific cation current dependent (bursting) pacemaker neurons (PM_{ICAN}). The relative contribution of each neuron type to rhythm generation depends on the state of the respiratory network, whether the network is in a “eupneic state”, “sigh state”, or “gasping state”. Experimentally these different respiratory network states can be studied in isolation because the preBötC responds to changes in oxygenation in a stereotypical manner that is comparable to the *in vivo* respiratory responses (Lieske et al., 2000; Pena et al., 2004; Hill et al., 2011). In well-oxygenated conditions, eupnea and spontaneous sighs are present, but during hypoxia the rhythm undergoes a biphasic response. Initially, fictive eupnea and sigh generation are augmented followed by network depression and the generation of fictive gasps. Upon reoxygenation, a post-hypoxic depression is entered in which all rhythm generation is silenced. This is followed by a post-hypoxic augmentation of the eupneic rhythm (Fig. 2A, (Blitz and Ramirez, 2002; Pena et al., 2004; Hill et al., 2011; Garcia et al., 2013a)). Moreover, this stereotypical post-hypoxic response can be mimicked by adding hydrogen peroxide, a reactive oxygen species and by-product commonly encountered during reoxygenation from hypoxia (Garcia et al., 2011).

These changes are the result of network reconfiguration and the intrinsic oxygen sensitivity of the preBötC. This concept, which becomes very relevant for understanding SIDS, is the notion that the respiratory network reconfigures from a network with heterogeneous network and membrane properties during eupneic activity into a much simpler, and thus more vulnerable, network state during gasping (Pena et al., 2004). During fictive eupnea, multiple non-pacemaker and pacemaker (bursting: PM_{ICAN} , and PM_{INaP}) neuronal types employ the use of both excitatory and inhibitory synaptic mechanisms to create multiple avenues by which the respiratory rhythm is generated. Thus, in well-oxygenated conditions, perturbation of a single rhythmogenic mechanism will not necessarily eliminate the eupneic rhythm

(Pena et al., 2004). The complexity and redundancy of this eupneic network state is one of the reasons why the question of whether pacemaker neurons or inhibitory mechanisms are “essential” for respiratory rhythm generation is still a matter of discussion and ongoing investigation (Ramirez et al., 2012). Indeed, most manipulations fail to stop respiratory rhythm generation under control conditions. Given the essential nature of breathing, redundancy of network mechanisms giving rise to breathing is clearly critical for survival. In the context of SIDS, redundancy is very important, as it explains why a vulnerable child breathes normally under control conditions. Any genetic predisposition or pathological abnormality that affects a component of the respiratory network would easily be compensated by other network, neuromodulatory, and membrane properties (Doi and Ramirez, 2008, 2010; Ramirez et al., 2012), thus maintaining normal respiratory rhythmic activity. However, as the respiratory network becomes exposed to hypoxia, rhythmogenesis transitions from this complex multimodal network state that characterizes eupnea to a much simpler, yet presumably more energy efficient, gasping state in which the respiratory network becomes entirely dependent on one particular rhythm generating mechanism, a mechanism that depends on PM_{INaP} (Pena et al., 2004). PM_{INaP} are hypoxia resistant (Fig. 2B) and as its name implies, autonomous bursts from PM_{INaP} are driven via the persistent sodium current (Pena et al., 2004). When the persistent sodium current is blocked, the fictive gasping rhythm, but not the eupneic rhythm is ablated from the preBötC, indicating that the gasping network state is dependent on PM_{INaP} (Pena et al., 2004; Pena and Aguilera, 2007; Hill et al., 2011).

2.4. Serotonin regulates pacemakers that are essential for gasping

The finding that PM_{INaP} neurons are essential for the generation of gasping has important implications for understanding SIDS. This dependency explains why gasping represents a vulnerable network state, while eupneic breathing does not. The vulnerability of the gasping state is best illustrated by its dependency on serotonin, a neuromodulator that has long been recognized as a key player in SIDS (Duncan et al., 2010). As our laboratory first demonstrated, bursting in PM_{INaP} neurons relies on the endogenous release of 5-HT acting on 5-HT_{2A} receptors (Pena and Ramirez, 2002). Blocking these 5-HT_{2A} receptors abolishes bursting in PM_{INaP} neurons. Thus, in the absence of endogenous serotonin activation, gasping at the network level is abolished (Tryba et al., 2006). This finding has been confirmed in intact animals using several approaches aimed at depleting serotonergic neuromodulation within the brainstem (Li and Nattie, 2008; Cummings et al., 2009, 2011; Penatti et al., 2011). Specifically perinatal loss of brainstem serotonin neurons compromises the ability of rats to survive (Cummings et al., 2009, 2011). Indeed serotonin abnormalities are one of the characteristic features of SIDS as has been documented in numerous publications (Kinney et al., 2003, 2011; Kinney, 2005; Broadbelt et al., 2011, 2012). Together these findings not only illustrate a direct mechanistic link between 5-HT deficiencies and impaired gasping in SIDS infants, but further confirm that the gasping network state is comparatively simpler to that of the eupneic network state as it lacks several of the redundant mechanisms that keep the eupneic rhythm stable and very plastic. Because only one rhythm generating mechanism is present during gasping, the organism becomes vulnerable to factors, such as serotonin, that control the PM_{INaP} neurons.

Interestingly, blocking the cellular mechanisms that give rise to bursting in PM_{INaP} neurons abolishes not only gasping, but also sighs (Pena et al., 2004). Indeed, intrinsic bursting that resembles the large amplitude bursts generated during sighs can be observed in some PM_{INaP} neurons (Tryba et al., 2008), and the same modulators that activate sighs also activate these PM_{INaP} neurons (Tryba et al., 2008). This opens up the possibility that a disturbance in the mechanisms that give rise to gasping may also affect the generation of sighs. However, it must be emphasized that the network generating sighs is far from simple

as it involves multiple synaptic and metabotropic cellular mechanisms (Lieske and Ramirez, 2006b,a).

2.5. The preBötC and cardio-respiratory control

Hypoxia affects not only breathing, but also the cardiovascular system. In infants and animal models, heart rate appears to initially increase during the same period when respiratory rate increases during hypoxia (Bamford et al., 1996; Horne et al., 2000; Nock et al., 2004; Horne et al., 2005; Hehre et al., 2008). As the respiratory rate decreases, bradycardia ensues with transient increases in heart rate during gasps (Hunt, 1992; Poets et al., 1999; Harper et al., 2000). This interaction illustrates the tight cardio-respiratory coupling produced through inspiratory-related phasic inhibition of parasympathetic input to the heart. Parasympathetic control over heart rate predominantly originates from cardiac vagal neurons of the nucleus ambiguus (CVN_{NA}). CVN_{NA} exist in the nucleus ambiguus at the level of the preBötC and are functionally coupled to preBötC rhythmogenesis, receiving inhibition in phase with the preBötC rhythm (Mendelowitz, 1999; Neff et al., 2004). Thus, in addition to the role for generating inspiratory rhythms, the preBötC appears to be critically important to cardio-respiratory coupling. Therefore, subtle abnormalities with the preBötC and the surrounding circuitry connected to CVN_{NA} may have a profound influence on the neurobiological basis of cardio-respiratory coupling which is important to arousal and auto-resuscitation efforts associated with SIDS.

2.6. The final common final pathway for multiple risk factors leading to SIDS

In addition to recognized deficiencies in serotonergic neuromodulation, several other biological risk factors have been identified upon postmortem study. Several of these factors include polymorphisms identified in infants who have succumb to SIDS and include TNF, aquaporin 4, various interleukins, pituitary adenylate cyclase activating polypeptide, hepatic glucose-6-phosphatase transporter, and cardiac ATP-sensitive potassium channels (Forsyth et al., 2005, 2007; Rand et al., 2007; Weese-Mayer et al., 2007; Ferrante et al., 2008, 2010a; Opdal et al., 2010; Tester et al., 2011). It is likely that these factors contribute to SIDS in ways that are independent of serotonergic mechanisms. Aquaporin 4 for example is permeable to CO₂ (Musa-Aziz et al., 2009). Thus, a mutation in this channel could have detrimental effects in chemosensation. Alternatively AP4 could disturb the regulation of water homeostasis as suggested by Opdal et al. (2010). Of particular interest is the finding that AP4 play a role in astrogliosis following microinfarcts (Wang et al., 2012). In this context these channels may be critical for water homeostasis and edema clearing (Zador et al., 2009; Saadoun and Papadopoulos, 2010). Gliosis is an important hallmark of SIDS (Kinney, 2009; Chiu et al., 2012). TNF α and various cytokines have also been linked to SIDS in several studies (Kadhim et al., 2003; Perskvist et al., 2008; Ferrante et al., 2010a,b; Vennemann et al., 2012); Disturbances in the pro-inflammatory cytokines could affect the homeostatic response of the respiratory network. It is for example known that various interleukins play a role in the response to hypoxic insults in general (Del Rio et al., 2012). Another important contributing mechanism may be related to a disturbed glucose metabolism. Of great interest is the finding that gene polymorphisms regulating glucose metabolism are also disturbed in SIDS (Forsyth et al., 2005). Glucose concentration affects the hypoxic response of the respiratory network and may contribute to the known gender difference in SIDS (Garcia et al., 2013b). Ultimately, all of these factors could disturb homeostatic mechanisms that are required for an adequate response of the respiratory network to respond to a challenge for example posed by the prone position. It will be interesting to learn how each of these factors affects the response of the respiratory network. Of specific interest is the question whether the reconfiguration of the preBötC from a robust, yet plastic state of eupnea to a vulnerable gasping state is particularly susceptible to the

aforementioned genetic predispositions leading to a disrupted gasping physiology and a final common pathway of failed arousal, failed autoresuscitation, and ultimately, SIDS (Fig. 3).

3. The influence of gender and age over cardio-respiratory function

3.1. Recognizing the epidemiological characteristics of gender and age in SIDS

SIDS has a well-recognized gender bias (Kinney, 2005; Trachtenberg et al., 2012) with male infants accounting for 60% of SIDS cases (Mage and Donner, 2009). Moreover, a review of the United States from 1979 to 2006 demonstrated that while the incidence of SIDS dramatically dropped after the Back-to-Sleep campaign, the male fraction of SIDS cases has remained at or very close to 0.61 (Mage and Donner, 2009). This consistent male bias in SIDS risk, despite significant changes in SIDS incidence, strongly argues for a biological origin in the SIDS gender bias. However, unlike the prone position, which arguably is strictly an external risk factor for SIDS (Lewak, 2012), the male gender appears to be an intrinsic risk factor related to several conditions involving respiratory distress.

During infancy, respiratory distress syndrome, bronchopulmonary dysplasia, accidental suffocation in bed, acute respiratory infection, and suffocation by inhalation of food or other foreign objects all have a male infant mortality fraction equal to 0.59 or greater, similar to the male infant mortality fraction in SIDS (Mage and Donner, 2009). Thus, male infants appear to be particularly vulnerable to disrupted respiratory function and distress. While it has been proposed that impaired arousal may play a role in the etiology of SIDS (Thach and Lijowska, 1996; Lijowska et al., 1997), arousal likely does not account for the gender difference in SIDS susceptibility. It was recently reported that no difference in the threshold or occurrence of either sub-cortical or cortical arousals was present between male and female infants (Richardson et al., 2010). Hypoxia, however, is a common denominator among each of the male-dominated respiratory distress conditions mentioned above. Furthermore, the fraction of male infant mortality in congenital cardiac abnormalities that involve hypoxic and/or ischemic insult is again similar to the fraction in SIDS (Mage and Donner, 2004). Thus, there is mounting epidemiological and experimental (see below) evidence that point to potential gender differences in physiology related to hypoxia and SIDS risk. In addition to gender, other epidemiological patterns have a recognized bias in the SIDS literature; one of the most prominent being age.

The age distribution of SIDS occurrence was first recognized by Raring in 1974 (Raring, 1974). More recently, using a data set containing approximately 20,000 SIDS cases throughout the world, Mage found that the age distribution of SIDS appears to follow a four parameter lognormal function (Mage, 1996). When described by this function, SIDS occurrence peaks between three and four months of age with a median age near 3.1 months. Developmental changes occurring during this high-risk period may be a key intrinsic factor contributing to SIDS susceptibility. While the epidemiological data clearly illustrate the influence of both age and gender on SIDS risk, how age and gender affect cardio-respiratory function to increase the susceptibility remains largely unknown. However, extensive experimental work on these issues has provided a great deal of insight into potential mechanisms by which age and/or gender may influence cardio-respiratory function.

3.2. Dissecting the influence of development and gender over mechanisms essential to cardio-respiratory control

Several aspects of respiratory physiology have gender specific traits and such concepts have been extensively reviewed elsewhere (For reviews: (Behan et al., 2003; Behan and Wenninger, 2008; Soliz et al., 2012; Joseph et al., 2013; Kinkead et al., 2013)). Because SIDS appears to have a gender bias with a distinct developmental profile this section focuses

on recent findings pertaining specifically to gender and developmental windows commonly used to investigate potential vulnerabilities that related to SIDS.

During discrete periods of development, respiratory control and function undergo changes both at the cellular and systems level (Wong-Riley and Liu, 2005; Holley et al., 2012; Garcia et al., 2013a). In rodents, the second postnatal week is a critical period of brainstem development when chloride homeostasis (Lee et al., 2005; Liu and Wong-Riley, 2012), NMDA receptor expression (Wong-Riley and Liu, 2005), and GABA_A receptor subunit expression (Liu and Wong-Riley, 2006) change. Such developmental changes may create specific windows of postnatal development when cardio-respiratory impairment may be exaggerated by a coinciding disruption in neuromodulation within the brainstem. For example, the fictive gasping rhythm originating from the preBötC is abolished in neonatal slice preparations when 5-HT_{2A} receptors are blocked (Tryba et al., 2006), yet blockade of 5-HT receptors in juvenile in situ preparations does not affect gasping (Toppin et al., 2007). Together these data suggest a transient developmental dependence of respiratory control on serotonergic neuromodulation. In further support of such a perspective, mice genetically deficient for Pet-1 have impaired serotonergic neuromodulation but gasping and auto-resuscitation are markedly attenuated only during a short window of postnatal development (Cummings et al., 2011). Moreover, pharmacological ablation of serotonergic neurons results in disrupted respiration accompanied by severe bradycardia in neonates during the first two postnatal weeks (Cummings et al., 2009). Chemosensitivity can also be affected by serotonin. In mice with disrupted serotonergic reuptake, hypercapnic chemosensitivity is disrupted as early as postnatal day (P) 15 (Penatti et al., 2011). Interestingly, this loss of chemosensitivity is biased toward the male gender (Li and Nattie, 2008; Penatti et al., 2011). Therefore, changes in the serotonergic network can potentially increase susceptibility to SIDS in both an age and gender dependent manner.

The SIDS age and gender biases, however, likely depend on a number of mechanisms. Holley et al. (2012) recently reported that male rats between P12 to P13 have suppressed ventilation in both normoxic and hypoxic conditions which correlated to greater circulating estradiol in males compared to females (Holley et al., 2012). Of particular relevance for SIDS is the study by Fournier et al. (2013), indicating that serotonin plays a critical role in linking maternal stress and anxiety during gestation to respiratory disorders in newborns. Specifically, gestational stress led to a significant reduction in medullary serotonin levels in newborns and resulted in increased respiratory instability and apneas. Moreover, the authors reported that apneic events could be reduced with 8-OH-DPAT, which was only significant in male pups. A gender-bias was also observed in another study. Treating neonatal rats with mifepristone, a progesterone and glucocorticoid receptor antagonist, resulted in an enhanced hypoxic ventilatory response biased toward males when tested between P10 and P12 (Fournier et al., 2012). Thus, these animal models indicated a potential prepubescent hormonal influence on respiratory function creating potential differences in respiratory function during hypoxia. For more examples the reader is referred to the review by Behan and Wenninger (2008). In addition to such differences, during hypoxia Garcia et al. (2013a) reported that during reoxygenation the post-hypoxic respiratory depression is significantly longer in males when compared to females at P10–13. This difference in post-hypoxic recovery appeared to involve the preBötC. While male preBötC rhythms were more likely to fail during hypoxic augmentation, during reoxygenation, male rhythms took longer to reestablish rhythmic bursting. Interestingly, the gender difference in post-hypoxic recovery of the preBötC rhythm appeared to have a developmental component as no differences in post-hypoxic recovery of rhythmogenesis were found prior to P10. The gender disparity in post-hypoxic recovery could be eliminated by pharmacological manipulation of ATP-sensitive potassium channels; conversely, glucose supplementation augmented the gender differences. These findings suggest that gender differences in post-hypoxic recovery of the

preBötC involve differences in metabolism. In concurrence with this finding, gender based variations in gene loci encoding enzymes involved with glycogen/glucose metabolism have been previously identified (Thach et al., 2009). It is clear that many mechanisms may contribute to the age and gender differences in SIDS. Understanding if and when each of these mechanisms has a functional role in SIDS vulnerability will be the next step in characterizing the physiological determinants of SIDS.

4. Prematurity and SIDS

4.1. Clinical background

Preterm birth remains a prominent although poorly understood risk factor for SIDS. The Back-to-Sleep campaign dramatically decreased the overall SIDS risk, but, like the gender bias, the risk associated with preterm birth has remained elevated (Malloy, 2004; Halloran and Alexander, 2006; Malloy, 2013). The failure of the Back-to-Sleep campaign to make solid gains in the preterm population is potentially due to an increase in preterm survival rates. Recent advances in neonatal care has increased the prevalence of extremely (<28 post-conception) and very (<34 post-conception) premature infants (Costeloe et al., 2012), populations that have the highest risk of SIDS compared to preterm infants born at later gestational ages (Malloy, 2013). The jump in these populations may have occluded gains obtained from the Back-to-Sleep campaign but also emphasize the need for a strong mechanistic understanding of the intrinsic factors that increase SIDS risk after preterm birth.

Why preterm birth increases SIDS risk is poorly understood. Initially respiratory difficulties such as apnea of prematurity were thought to predispose preterm infants to SIDS. It has been since shown, however, that the presence or absence of apneas and periodic breathing does not predict SIDS risk for preterm infants (Southall et al., 1982; Hoffman et al., 1988; Hodgman, 1998; Baird, 2004). Although contrary, this finding does not preclude the importance of breathing disorders (Kahn et al., 1993; Poets et al., 1995; Franco et al., 1998; Constantin et al., 1999; Goto et al., 1999). Most preterm infants have chronic and/or acute periods of low arterial oxygen levels due to breathing instability and immature lung function (Henderson-Smart, 1981; Colin et al., 2010; Smith et al., 2010; Holstein et al., 2011). In many cases, mechanical ventilation and/or continuous positive air pressure (CPAP) are used to stabilize blood gas levels. Mechanical ventilation, however, can cause damage to the airway passages and lungs, while both mechanical ventilation and CPAP increase the risk of lung infection (Mokres et al., 2010; Jobe, 2011). Furthermore, during the first week of life, high oxygen saturation targets increase oxidative stress and the risk of bronchopulmonary dysplasia (Saugstad, 2010; Askie, 2013; O'Reilly et al., 2013). All of these outcomes can potentially decrease oxygen levels. SIDS may therefore be associated with early periods of low oxygen saturation regardless of the presence or absence of respiratory instability. These challenges may alter developing autonomic function in preterm infants (Yiallourou et al., 2013). Chronic and intermittent hypoxia also increase fetal hemoglobin levels, decreasing baseline levels of available oxygen, and has been associated with an increased risk of SIDS in some (Bard, 1992; Bard et al., 2003; Richardson et al., 2004) but not all (Krous et al., 2007) studies.

One glaring omission from the SIDS literature is how different underlying causes of preterm birth may influence SIDS risk. Although there is extensive data on prenatal nicotine exposure which increases the risk of both SIDS and preterm labor (Shea and Steiner, 2008; Einarson and Riordan, 2009; Abbott and Winzer-Serhan, 2012; Malloy, 2013), maternal inflammation, the main cause of preterm labor, has been largely ignored as an area of research. Maternal inflammation can cause dopamine and serotonin deficiencies in the frontal cortex and hippocampus among other brain areas of offspring (Wang et al., 2009). Similar changes in the brainstem serotonergic system would be of particular interest since

altered serotonergic function has been found postmortem in infants succumbing to SIDS (Panigrahy et al., 2000; Kinney et al., 2003; Kinney, 2005; Paterson et al., 2006; Duncan et al., 2010; Broadbelt et al., 2011) and after prenatal nicotine exposure in both infants (Duncan et al., 2009) and animal models (Slotkin et al., 2011). Most studies on maternal and fetal inflammation, however, have been focused on Parkinson's disease and cannot be readily generalized to preterm SIDS research. Furthermore, little research has addressed how preterm birth combined with additional risk factors such as prenatal nicotine exposure or bronchopulmonary dysplasia affect susceptibility. Two studies suggest that these additional factors may increase SIDS risk within the preterm population (Calder et al., 1994; Sawnani et al., 2004).

Regardless of which predisposing condition(s) increases SIDS risk in preterm infants, it is a mistake to equate a preterm infant to a term infant even after correcting for gestational age. Preterm infants are forced to transition to air breathing when they are physiologically ill-equipped and therefore have to use different strategies to stabilize respiration (Carroll and Agarwal, 2010; Smith et al., 2010). Mechanical and drug interventions will also alter postnatal respiratory development (Sweet and Halliday, 2005; O'Reilly et al., 2013). Intriguing epidemiological findings from two groups have shown that preterm infants succumb to SIDS at earlier post-conceptional ages than term infants (45 versus 55 weeks, respectively) but later postnatal ages (20 versus 15 weeks, respectively) (Halloran and Alexander, 2006; Malloy, 2013). This distinct high-risk time period should not only be a consideration while conducting preterm studies, but may also be used to identify developmental changes correlated with SIDS risk in preterm versus term populations.

4.2. A need for animal models

Unfortunately, there is currently no appropriate animal model combining preterm birth and SIDS. It may be possible however to draw some parallels between prenatal nicotine exposure and preterm birth. Research in this area has focused on physiological responses to air challenges. In term infants, normal biphasic responses to hypoxia were present at 2–5 weeks, 2–3 months, and 5–6 months postnatal (Richardson et al., 2007; Verbeek et al., 2008). In preterm infants, the ventilatory response to hypoxia appears to transition from a monophasic depressive response at 31.5 weeks post-conception (Alvaro et al., 1992) to a biphasic response by 35.5 weeks post-conception (Martin et al., 1998) and is still present at 45 weeks post-conception (Verbeek et al., 2008). The early monophasic depressive response may reflect the transition from fetal-like to neonatal respiratory and autonomic function in preterm infants (Boddy et al., 1974; Alvarez et al., 1992) and is similar in some ways to the attenuated ventilatory augmentation seen in anesthetized infants and animal models after prenatal nicotine exposure (Ueda et al., 1999; Hafstrom et al., 2002; Sawnani et al., 2004; Eugenin et al., 2008). In the *in vitro* preBötC preparation, prenatal nicotine also attenuated the initial augmentation during hypoxia and impaired in the ability to maintain fictive gasping during severe hypoxia (Hu et al., 2012).

In addition, term infants maintained higher oxygen levels than preterm infants when exposed to mild hypoxia at 2–5 weeks adjusted postnatal age (Horne et al., 2002; Verbeek et al., 2008). Likewise, at 1–3 months of age control infants had lower drops in oxygen saturation when exposed to hypoxia/hypercapnia than infants of smoking mothers (Campbell et al., 2001). It is also interesting to note that during hypoxic challenges, preterm infants have greater drops in oxygen saturation early in life (2 weeks to 3 months) compared to later (5–6 months), while term infants tend to maintain oxygen saturation early (2–3 weeks) and become more sensitive at later ages (2–6 months) (Horne et al., 2002; Richardson et al., 2007; Verbeek et al., 2008). Differences such as these may help to account for the earlier occurrence of SIDS in preterm infants. Many studies have also shown impaired arousal in both preterm (Horne et al., 2000; Ariagno et al., 2006; Verbeek et al., 2008) and nicotine

exposed infants (Lewis and Bosque, 1995; Richardson et al., 2009; Franco et al., 2011) in a sleep-state and age dependent manner.

4.3. Cardio-respiratory coupling

Cardio-respiratory coupling is also altered after both preterm birth and prenatal nicotine. In the case of preterm birth, it appears that cardio-respiratory coupling is not fully developed resulting in lower heart rate variability (Reulecke et al., 2012). Decreased cardio-respiratory coupling was also associated with lower O₂ saturation within a preterm population (Elder et al., 2010). During hypoxia, underdeveloped cardio-respiratory coupling would blunt respiratory-induced increases in heart rate and may diminish the ability to arouse and autoresuscitate. In prenatal nicotine animal models, altered cardio-respiratory coupling is also observed and results in immediate and severe bradycardia during hypoxia. Normally, cardiac vagal neurons in the nucleus ambiguus (CVN_{NA}) are inhibited during inspiration. After prenatal nicotine, inspiratory-related inhibition is reduced during hypoxia resulting in greater parasympathetic input to the heart (Neff et al., 2004; Evans et al., 2005). Decreasing the inspiratory-related inhibition may be somewhat analogous to the underdeveloped cardio-respiratory coupling seen in preterm infants. However, during hypoxia/hypercapnia prenatal nicotine also recruits an aberrant excitatory inspiratory-related input to the CVN_{NA} (Evans et al., 2005; Huang et al., 2005) this additional factor may provide some insight to the very high risk prenatal smoking poses for SIDS.

5. The intersection of arousal, central chemosensitivity, auditory function

5.1. Auditory findings and their potential link to SIDS

As discussed earlier, inspired CO₂ and end-tidal CO₂ are significantly elevated in children sleeping in the prone position indicating that SIDS victims may not respond appropriately to hypercapnia (Chiodini and Thach, 1993). Moreover, post-mortem examination of tissue from SIDS victims identified decreased serotonergic receptor binding distributed throughout several regions of the brainstem implicated with autonomic control over respiratory function (Panigrahy et al., 2000). While these brainstem areas are important to central chemosensitivity and respiration, they are also important to the integration of several forms of autonomic control including cardiovascular function, sympathovagal tone, and vestibular function all of which are implicated in shaping the arousal response. Hence, deficiencies in central chemosensitivity may only be one physiological aspect affected in SIDS vulnerable infants with deficits in arousal.

In an intriguing case-controlled study by Rubens et al., retrospective comparison of newborn transient evoked otoacoustic emission (TEOAE) hearing screens between infants who had succumbed to SIDS and infants surviving the first year of life found that SIDS infants had significantly lower signal to noise ratio at 2, 3 and 4 kHz (Rubens et al., 2008). This study became the driving force behind subsequent work examining the clinical relationship between auditory function and SIDS. However, Farquhar and Jennings reported no differences between the rates of hearing loss in SIDS cases versus all births within the state of Michigan during the same period (Farquhar and Jennings, 2008). In perhaps the largest study to date addressing the relationship between SIDS and auditory function, Chan et al. (2012) tested otoacoustic emission (OAE) in 521 infants and then predicted which infants were at risk for SIDS. The risk rate obtained from OAE testing was then compared to SIDS incidence within the same region. These authors found that risk rate obtained by OAE testing was greater than the published SIDS rate. OAE testing therefore produced a large number of false positives suggesting that auditory testing alone is not a good predictor for SIDS (Chan et al., 2012). However, neither of these more recent studies can refute the

potential physiological implication that abnormal auditory/vestibular function may be a prevalent trait in infants at risk for SIDS.

5.2. The vestibular nucleus and its potential link to SIDS

Allen et al. developed an experimental mouse model that uses gentamicin-induced loss of hair cells in the inner ear to examine the potential relationship between auditory/vestibular and respiratory physiology (Allen et al., 2011). These gentamicin-exposed mice exhibited an attenuated ventilatory response to a hypercapnic stimulus. Post-mortem histological analysis revealed a decrease in hair cell number accompanied with a decrease in the number of large neurons within the lateral vestibular nucleus and no discernible changes in the cochlear nucleus (Allen et al., 2011). These findings not only support the potential interaction between hair cell loss and attenuated responses to respiratory stimuli, but also suggest that the mechanism leading to this deficit may involve the central nervous system at the level of the vestibular nucleus (VN).

Previous reports have shown that vestibular stimulation increases respiration (Monahan et al., 2002; Miyamura et al., 2004). Interestingly, a recent study by Quintana et al. (2012) showed that genetic inactivation of *Ndufs4*, which encodes for a mitochondrial protein important to the function of complex I, caused significant lesioning in the VN and attenuates the ventilatory response to hypercapnia. The group also demonstrated that the restoration of *Ndufs4* in the VN of *Ndufs4* knockout mice rescued the ventilatory response to hypercapnia (Quintana et al., 2012). In aggregate, the findings from these experimental models indicate that the VN plays a significant role in generating central chemosensitivity to CO₂. However, the specific role of the VN in CO₂ central chemosensitivity is still largely unknown. For example, are VN neurons intrinsically sensitive to CO₂ and/or acidification or do VN neurons play a key role in relaying or coordinating information throughout the brainstem? Either case is possible as electrical stimulation of VN modulates firing properties of preBötC neurons (Zheng et al., 1997; Holstein et al., 2011).

In summary, while the observed histological brainstem deficits of SIDS infants may be indicative of respiratory dysfunction, other physiologies may also be subtly affected. For, example, although perinatal hearing/vestibular impairment by itself may not be robust predictor of SIDS vulnerability, there is an emerging possibility that hearing/vestibular function may be impaired in SIDS vulnerable infants. However, the precise role of the VN in central chemosensitivity and SIDS remains an open issue. Thus, a clear need exists for a more comprehensive neurophysiological understanding between central vestibular and central respiratory control.

6. Conclusions

Several critical but avoidable risk factors for SIDS have been identified, dramatically reducing SIDS incidence. However, SIDS remains a serious problem underscoring the need for a better understanding of the underlying causes. Anatomical evidence indicates that SIDS is associated with specific pathological abnormalities in the medulla involving neuromodulators known to be involved in the neuronal control of breathing. Hence, the next step is to unravel how these pathologies and risk factors combine to contribute to a child's death. In this review we discussed the physiological determinants that make a child vulnerable to the known risk factors. Importantly, these physiological determinants align with the identified pathologies. What emerges is a more complete picture that better defines the factors characterizing a vulnerable infant and points toward a final common pathway (Fig. 3) which leads to the infant's inadequate response to environmental challenges. This understanding provides an important framework that will enable us to better define how

other risk factors lead to SIDS. We regard this as an important step toward identifying novel avenues to prevent SIDS and further reduce SIDS incidence.

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Fig. 1.

Arousal and autoresuscitation follow stereotypical patterns that protect infants sleeping in the prone position from SIDS. Brainstem abnormalities, however, may alter preBötC network and impair sigh and gasp generation which may increase SIDS vulnerability. During prone sleeping, re-breathing exhaled air can increase CO₂ and decrease O₂ levels. The altered blood gas composition initiates the arousal response that begins with sigh generation during continued eupneic breathing. Successful arousal results in head lifting and repositioning which relieves the build-up of CO₂ and replenishes the O₂ supply. If arousal fails, a more severe hypoxic state is reached and eupneic breathing will transition to gasping. This transition is mediated by network reconfiguration of the preBötC (Lieske et al., 2000; Pena et al., 2004). Gasping is an autoresuscitation response that can lead to arousal and a return to normal blood gas levels. Should an infant fail to both arouse and autoresuscitate, the irreversible hypoxic insult leads to asphyxiation and the occurrence of SIDS.

Fig. 2.

The preBötC is a multi-functional network critical for generating the respiratory network response to hypoxia. (A) Even in the reduced state of an isolated brainstem slice, the preBötC is dynamically responsive to hypoxia and reoxygenation. Fictive eupnea (inset: red trace) produced in well-oxygenated states, fictive sighs (inset: yellow trace) triggered during the transition to hypoxia, and fictive gasps produced during steady state hypoxia (inset: blue trace). The generation of these in vitro patterns represents distinct network states determined by the integration of synaptic and intrinsic membrane properties of the neurons actively participating in each state. (B) The preBötC is comprised of a heterogeneous population of neurons that can be readily identified in synaptic isolation (Pena et al., 2004): non-pacemaker neurons, such as autonomous spiking neurons (top, gray box), PM_{ICAN} (middle, yellow box), and PM_{INaP} (bottom, blue box). Hypoxia silences both autonomous spiking neurons (i.e., non-pacemaking neurons) and PM_{ICAN} neurons but not PM_{INaP} neurons which demonstrates how the gasping network state lacks the redundancy present in the eupneic network state.

Fig. 3.

The final common pathway for SIDS involves a failure to arouse and autoresuscitate in response to environmental challenge. Many intrinsic and extrinsic factors increase SIDS susceptibility including gender, genetic polymorphisms, prenatal nicotine exposure, and temperature. These risk factors can directly alter the function of the preBötC and impair the ability of this network to generate sigh and gasping rhythms, as well as coordinate cardiorespiratory coupling between the preBötC and Nucleus Ambiguus. Thus, the function of the preBötC appears to be an important physiological determinant for SIDS.