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Potential Mechanisms of Failure in the Sudden Infant Death Syndrome

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Abstract

Current evidence suggests that multiple neural mechanisms contribute to the fatal lethal event in SIDS. The processes may develop from a range of otherwise seemingly-innocuous circumstances, such as unintended external airway obstruction or accidental extreme flexion of the head of an already-compromised structure of the infant upper airway. The fatal event may occur in a sleep state which can suppress muscle tone essential to restore airway patency or exert muscle action to overcome a profound loss of blood pressure. Neural processes that could overcome those transient events with reflexive compensation appear to be impaired in SIDS infants. The evidence ranges from subtle physiological signs that appear very early in life, to autopsy findings of altered neurotransmitter, including serotonergic, systems that have extensive roles in breathing, cardiovascular regulation, and thermal control. Determination of the fundamental basis of SIDS is critical to provide biologic plausibility to SIDS risk reduction messages and to develop specific prevention strategies.

Keywords

Apnea; brainstem; cerebellum; chemoreception; hypotension; serotonin

INTRODUCTION

Any discussion of mechanisms underlying the Sudden Infant Death Syndrome (SIDS) needs to relate those processes to the developmental period of most risk (2–4 months), state of the infant during the fatal event (during sleep, or in close proximity to a sleeping period), and ancillary circumstances (enhanced risk with prone sleeping position, diminished risk with use of a pacifier, and increased risk with prenatal exposure to tobacco, alcohol, and other drugs of abuse). All of these factors contribute to risk of an event that occurs suddenly in an otherwise "healthy" infant, i.e., without obvious cause after autopsy and examination of the death scene [1]. Subtle indicators of risk appear as early as within a few days after birth in infants at risk for SIDS or who later succumb to SIDS, manifested, among other characteristics, as distortions in sleep state organization, periods of tachycardia, diminished influence of respiratory modulation of heart rate, a loss of momentary respiratory pauses, an increased incidence of obstructive apnea, and decreased overall motility [2–8]. Although

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those indicators provide insights into underlying pathology, the characteristics are rather inconspicuous, with none being so extreme as to seemingly precipitate a fatal event, particularly as isolated events.

The suddenness of the final event suggests a process of catastrophic failure of ventilation or cardiovascular collapse. Although numerous theories about the potential mechanisms resulting in SIDS have been put forward since the original NIH definition in 1969, the most enduring and widely accepted is the cardiorespiratory hypothesis involving central mechanisms [9–14] (Table **1**). The hypothesis concerning central (brain) mechanisms of cardiorespiratory failure, the focus of this review, has been considerably strengthened over the years by: 1) normative physiological data indicating the first year of human postnatal life, particularly the first six months, is a vulnerable/critical period in the development and integration of central cardiorespiratory control; 2) abnormal physiological data in infants at risk for SIDS or who subsequently die of SIDS (in prospective studies) indicating subclinical deficits in autonomic function, respiration, and/or arousal; 3) neuropathologic studies of infants dying of SIDS indicating abnormalities in brain regions involved in cardiorespiratory control; and 4) an explosion in our understanding of central cardiorespiratory and arousal mechanisms at the molecular, cellular, neurochemical, and systems level through the neuroscientific analysis of human neuroimaging, whole animal models, reduced (brainstem) preparations, and cell culture [15–20]. Cardiovascular failure results from arrhythmia or other centrally-mediated autonomic processes, especially shock, culminating in hypotension with failure to perfuse vital organs. Failure of ventilation results from external airflow blockage or upper airway obstruction, loss of the drive to breathe, or failure of gasping to recover from hypoxic or hypoxemic events. An important issue for understanding SIDS mechanisms is that “cardiovascular” or “respiratory” failures are not mutually exclusive: rather, breathing mechanisms interact with the cardiovascular system. Consequently, a loss of blood pressure immediately triggers enhanced breathing efforts to restore vascular integrity (in addition to tachycardia and enhanced muscle tone). A transient increase in blood pressure, on the other hand, suppresses respiratory muscle tone [21], and does so preferentially to the upper airway musculature [22] possibly precipitating central apnea in the case of both diaphragmatic and upper airway muscle atonia, or an obstructive event if the suppression is principally to the upper airway. SIDS appears to result from a combination of circumstances of an exceptional cardiovascular or respiratory challenge, occurring in a compromised infant at a particular period of development [12]. The triad of conditions suggests that evaluation of neurotransmitter abnormalities that could interfere with multiple physiological aspects in SIDS infants would be valuable. The subsequent discussion considers cardiorespiratory processes in detail, with an emphasis on brain mechanisms that lead to cardiorespiratory failure, or alternatively, fail to give rise to compensatory mechanisms that overcome cardiovascular or respiratory failure. Evidence is drawn from physiological of infants at risk of dying of SIDS and neuropathological studies of SIDS infants, as well as developmental conditions such as congenital central hypoventilation syndrome (CCHS) which illustrate physiological characteristics relevant to the investigation of defective central cardiorespiratory mechanisms in SIDS [23].

CARDIOVASCULAR MECHANISMS

Cardiovascular collapse may be a scenario for SIDS based on evidence from physiologic characteristics detected by monitoring in infants who subsequently die of SIDS in days prior to and the moments immediately preceding the fatal event [9, 10, 24, 25]. Findings in such infants include a high incidence of tachycardia-bradycardia sequences before central respiratory efforts cease, a sequence that parallels the two-stage initial sympathetic followed by parasympathetic activity pattern in shock [26]. Cardiovascular collapse has been suggested as a failure mechanism in rare cases of SIDS where blood pressure was shown to

be impaired prior to the fatal event [27]. Signs of autonomic dysregulation appear in SIDS infants in the days and weeks prior to the SIDS event, including trains of tachycardia [28], increased numbers of autonomic, but decreased full (i.e., with EEG activation) arousals [29], profuse sweating (i.e., excessive sympathetic activation), and reduced respiratory-related heart rate variation [30]. An absence of short respiratory pauses, which are most likely a consequence of momentary blood pressure effects on breathing, has also been noted [6, 21, 31, 32]. Overheating has often accompanied the fatal event [33]; vasodilation associated with overheating makes compensation for low blood pressure more difficult. A primary risk factor for SIDS, the prone sleeping position, diminishes vestibular contributions to blood pressure recovery from hypotension [34, 35], and hampers heart rate and breathing compensation to such blood pressure manipulations as head-up tilt [36–38]. Vestibular influences on responses to pressor, hypercapnic, and hypoxic challenges are largely mediated through the cerebellar cortex and deep nuclei [39, 40]. Several processes can induce a shock or shock-like sequence; the most common causative processes being blood loss, infection or deep visceral pain or irritation. Blood loss can be ruled out in SIDS, but visceral irritation [10] or shock following infection remain possibilities; the relationship of infection to SIDS is being actively pursued [41].

Arrhythmia

A more-commonly postulated process for cardiovascular collapse is cardiac arrhythmia, with congenital prolonged QT syndrome a principally-proposed mechanism [42, 43]. Prolongation and variability in QT interval develops from mutations in any of several genes, each of which encodes cardiac ion channels [11]. The potential for induction of excessively-prolonged QT intervals is enhanced with excessive sympathetic outflow, with such expression resulting in a potentially fatal arrhythmia of torsades de pointes which can degenerate into ventricular fibrillation [44]. Nearly 10% of a sample of Norwegian SIDS infants showed genetic predispositions for prolonged QT intervals [45]. Genetic cardiac channelopathies are now thought to account for 5–10% of infants who die suddenly, i.e., fall under the rubric of sudden and unexpected infant death (SUID). Given that a specific cause of death has now been determined in these infants, they are no longer classified as SIDS, but rather as explained deaths [11] Nevertheless, it is possible that a larger proportion of SIDS deaths will ultimately be related to a cardiac arrhythmia with continued molecular research in SIDS. Even if SIDS infants have not inherited the genetic processes which lead to prolonged QT intervals, it is important to emphasize that generation of the sympathetic processes that contribute to cardiac arrhythmia can depend on excessively-activated central autonomic processes derived from seizure discharge [46], or from damaged brain structures which normally limit sympathetic and parasympathetic outflow or regulate extent of output in each system [47]. Several central structures limit sympathetic outflow and recovery from hypotension, among which are brainstem and cerebellar areas. Damage to the fastigial nucleus, the major autonomic roof nucleus of the cerebellum, can lead to death from hypotension in animal models [47]; Other models of exaggerated sympathetic tone [23] show significant cerebellar injury upon neuroimaging studies [48] and long QT intervals [49].

Although a set of findings suggests that SIDS results from a “cardiovascular failure”, spontaneous restorative mechanisms from cardiovascular collapse often depend on respiratory efforts, frequently exaggerated, such as gasping. Indeed, the capacity of the autonomic system to interact with breathing processes is critical to recovery. Thus, deficiencies in breathing mechanisms, or interactions between breathing and cardiovascular processes, must be considered in any fatal failure mechanism. Moreover, the integrated nature of the vital functions suggests the usefulness of considering overall regulatory systems affecting both vital processes.

RESPIRATORY FAILURE

External Airway Obstruction

A potential threat to infant survival develops with failure to recover from external airway obstruction, such as facedown positioning in a pillow or other soft bedding, resulting in excessive carbon dioxide (CO_2) exposure and hypoxia [11, 50]. Active promulgation of the "Back-to-Sleep" message, i.e., recommendation to place infants supine for sleep, has contributed substantially to the decline in the SIDS rates in recent years. The supine sleep position reduces the propensity for external airway obstruction. The mechanism of failure from such obstruction is thought, at least in part, to result from a developmental or potentially acquired inability to appropriately self-position the head and airway for free gas exchange. The loss of head movement can stem from several processes, including impaired carbon dioxide (CO_2) or oxygen (O_2) sensing, i.e., inadequate detection of extreme hypercarbia or hypoxia, due to deficits in central processing systems, deficient integration of sensory processes with appropriate motor reflexes, and/or failure of arousal mechanisms to restore motor tone or activate appropriate motor responses. Inadequate CO_2 or O_2 sensing or integration is an intense focus of investigation, with aberrations in development of neurotransmitter systems involved in that signal transduction, including prenatal nicotine exposure that can modify neurotransmitter development, or early hypoxic exposure which can "condition" or otherwise adapt afferent systems (see below). Multiple motor integrative systems participate in recovery from external airway obstruction, including structures in the brainstem. Another possibility involves cerebellar structures, since a principal function of the cerebellum is coordination of motor activity, including certain reflex actions.

Upper Airway Obstruction

Upper airway obstruction results from loss of tone to the upper airway musculature in association with continued diaphragmatic movements. These movements, in turn, generate repetitive negative thoracic pressures, enhancing airway collapse through the Venturi principle of accelerated airflow through a reduced diameter passage [51, 52]. Atonia of respiratory muscles can be induced by rapid transient elevation of blood pressure [21]; such atonia is preferentially exerted on the upper airway relative to the diaphragm [22]. The consequence is that impaired blood pressure responses to challenges can exert unexpected effects on breathing. Repeated obstructive events pose a significant risk for infants, first, from multiple exposures to intermittent hypoxia with successive obstructions, and secondly from repeated extreme changes in arterial pressure. The potential for obstruction is enhanced by atonia of the upper airway musculature during rapid eye movement (REM) sleep, a condition in which most of the body musculature, with the exception of the eye musculature and the diaphragm, lose tone. Rapid eye movement sleep also imposes an additional risk for breathing in infants, since intercostal muscles lose tone during that state. Since the ribs require a period of time to calcify, the intercostal muscles provide much of the stiffness of the infant thoracic wall cage. However, the atonia of intercostal muscles during REM sleep increases compliance, resulting in a "floppy" thoracic wall that collapses with each inspiratory effort [53]. The thoracic wall collapse leads to a substantial loss of intrathoracic volume with inspiration, leaving very little room for inspired air. The result is a potential for rapid desaturation with any process that might interfere with airflow, such as airway obstruction. Thus, the natural atonia of intercostal muscles during REM sleep introduces circumstances which can enhance SIDS risk. The potential for upper airway obstruction is also enhanced by the unique structure of the upper airway in the infant, with a relatively large tongue and airway dimensions which predispose to obstruction, particularly if the head is flexed, as shown by Tonkin [54] That head position can be particularly a risk condition from certain body positions for sleeping in automobile seats that allow extreme forward head flexion [55]. The circumstances under which head flexion in a developmentally

"normal" but morphologically-compromised airway, combined with the atonia of REM sleep state, leads to a fatal event could be considered accidental, but may be further compromised by deficient hypoxia-sensing or motor reflex pathways, possibly involving brainstem and/or cerebellar processes.

Central Apnea

Failure of respiratory drive to both upper airway and diaphragmatic musculature, or central apnea, has occupied a central focus for attention in proposed mechanisms underlying the fatal event in SIDS. That failure can result from several components of the breathing process, including impaired sensory transduction or integration of either CO_2 or O_2, or non-recruitment of gasping mechanisms, the final restorative mechanism to low oxygen. Since breathing failure is presumed to occur during sleep, a principal concern is loss of the "wakefulness drive to breathe," i.e., the waking state activates processes which maintain breathing, while during sleep; those influences are suppressed, or not recruited. A consistent loss of drive to breathe during sleep, especially during quiet sleep, occurs in congenital central hypoventilation syndrome (CCHS) [23], a rare disorder resulting from mutation of PHOX2B, a gene responsible for cell differentiation, with autonomic ganglia and neurons near the parafacial nuclei especially affected, as well as maldevelopment of the locus coeruleus, nucleus of the solitary tract, and retrotrapezoid nucleus at the ventral medullary surface [15, 56–60]. In addition to hypoventilation during sleep, breathing in CCHS infants is unresponsive to higher levels of CO_2 or low O_2. CCHS is not a model for SIDS, since, although a PHOX2B polymorphism appears in SIDS infants, that polymorphism is unrelated to that found in CCHS [61, 62], and affected CCHS infants show a wide range of profound autonomic deficiencies much more extreme than apparent in SIDS infants prior to death. However, impaired central chemosensitivity and breathing drive during sleep are major concerns in SIDS, and the loss of central chemosensitivity provides a useful model to illustrate processes other than chemical drive which contribute to maintaining breathing. Moreover, by comparing brain responses to high CO_2 in CCHS and control children, brain structures involved in mediating neural responses to chemoreception can be determined.

The implications from CCHS studies for understanding SIDS mechanisms are that processes used to sustain breathing depend on multiple inputs, including thermal, affect, and kinesthetic cues, in addition to chemosensitive input and intrinsic oscillatory activity of medullary structures. Moreover, contributions from different influences vary by sleep or waking state; temperature drive to breathe, for example, is lost during REM sleep [63], and control of ventral medullary surface neural structures on blood pressure are altered during that state [64]. The atonia of REM sleep modifies upper airway and other muscle function, and hence, kinesthetic feedback. CCHS breathing deficiencies appear preferentially during quiet sleep; REM sleep is more protected, again indicating that determination of mechanisms underlying breathing requires consideration of influences from forebrain as well as medullary sites. The implication for SIDS from CCHS studies is that both rostral brain and brainstem mechanisms are involved in breathing control, and different mechanisms may contribute to state-related drive to breathe. Of note, a recent in-depth neuropathologic case study of Haddad syndrome (CCHS combined with Hirschsprung's disease) revealed hypoplasia of the locus coeruleus which mimics that seen in Phox2b knockout mice, in addition to other brainstem and forebrain developmental anomalies [65].

Gasping

The final defense to hypoxic exposure is gasping, a sequence of respiratory efforts triggered by activation of structures in the brainstem. Gasping is frequently found in monitored respiratory signals in infants who succumb during home monitoring [25]. Because a successful outcome to gasping is obviously vital, determining the underlying triggering and

neuromodulatory processes for this respiratory pro-cess are objects of considerable interest. Blockade of 5-HT and noradrenergic receptors suppresses gasping; 5-HT alone appears to be less effective, suggesting that an integrated participation of multiple systems triggers gasping efforts [66, 67].

AROUSAL MECHANISMS AND CARDIORESPIRATORY CONTROL

A pervasive aspect through all attempts to understand mechanisms underlying SIDS is that the fatal event apparently occurs during sleep, with the possibility that restoration of the "wakefulness" stimulus has the potential to restore vital function. The processes underlying arousal are complex, since "arousal" exists at several neuroanatomic levels, from activation of muscle tone, autonomic regulation, electroencephalographic activity, and cognition. Each of these processes differs in underlying neural pathways and neurotransmitter action, many of which interact to produce an integrated response. Normally, arousal processes are integrated in time, with near-simultaneous recruitment of muscle activity, autonomic enhancement, such as heart rate and blood pressure, and electroencephalogram activation [68]. However, individual components of the arousal process can be separated, showing that arousal is not a unitary phenomenon. Electroencephalographic (EEG) synchronized slow wave activity can appear in cortical structures in an alert animal with atropine-induced cholinergic blockade [69], desynchronized EEG activity appears in REM sleep, and cognitive processes can be blocked during waking by serotonergic blockade [70]. Different components of the arousal response emerge in infant sleep, with SIDS infants showing more "autonomic" arousals and fewer "full" arousals, *i.e.*, with cortical desynchronization [29]. The implication for SIDS is that an "arousal" failure has the potential to result from impaired action in any of a number of separate systems.

BRAIN STUDIES IN SIDS INFANTS RELEVANT TO THE CENTRAL CARDIORESPIRATORY HYPOTHESIS

The central cardiorespiratory hypothesis in SIDS has led to multiple neuroanatomic studies of relevant brain regions in SIDS infants at autopsy [11, 12, 71, 72] (Fig. **1**). The dilemma of brain research in SIDS, however, is that the brains in general "look normal" under the light microscope, the tool of standard histopathology. At the very most, there are nonspecific and subtle indications of cell injury that are not limited to cardiorespiratory related regions. Moreover, certain abnormalities may reflect secondary consequences of chronic, prior, or repetitive hypoxia-ischemia, e.g., apoptosis and microglial activation in the hippocampus, brainstem gliosis and apoptosis, periventricular leukomalacia, cerebral white matter gliosis, and cerebral cortical injury, recently reviewed in depth [11, 72]. In addition, certain brain abnormalities suggest subtle developmental anomalies originating *in utero* that may point to abnormal maturational factors in the overall neuropathology of SIDS [72], e.g., increased number and density of leptomeningeal neurons [73]. The overall cardiorespiratory hypothesis of brain studies in SIDS is that there are lethal abnormalities in one or more brain structures critical for state-dependent autonomic and respiratory control in SIDS infants at autopsy which are detectable only by quantitative and/or special molecular, cellular, and/or neurochemical research tools at autopsy. To date, virtually all cardiorespiratory-related brain regions have been scrutinized in SIDS infants, including the brainstem, cerebellum, hypothalamus, and hippocampus, as recently reviewed by us [11, 12, 71, 72] (Fig. **1**). Here we highlight neuropathologic findings in two brain regions that have received perhaps the greatest attention, i.e., the brainstem and cerebellum. Of note, the potential definition of SIDS-specific neuropathology in arousal-related pathways is a special challenge, because virtually all of the principal identified neurotransmitter systems in the brain are involved in arousal responses, with the major participation of cholinergic, adrenergic, serotonergic (5-HT), and dopaminergic neurotransmitter systems, and a range of neuropeptides, including

orexin (hypocretin) [17]. Neural structures responsible for arousal characteristics also lie in multiple brain areas, especially the basal forebrain, hypothalamus, and brainstem (ventral tegmental area of Tsai, lateral tegmental pons, locus coeruleus, and midline raphé). Future research is needed in SIDS brains that attempts to integrate potential pathologic findings across these widespread and diverse neurochemical and neuroanatomic systems.

Brainstem Findings in SIDS Infants and the Central Cardiorespiratory Hypothesis

To date, the most robust, reproducible, and in-depth findings related to the central cardiorespiratory hypothesis in SIDS have been reported in SIDS brainstems, as recently reviewed by us [12, 72] (Fig. **1**). These abnormalities involve (although are not necessarily specific to) regions critical to central cardiorespiratory control, modulation, and/or integration. These regions include the hypoglossal nucleus (airway patency, particularly during sleep), nucleus of the solitary tract (visceral sensory input), dorsal motor nucleus of the vagus (preganglionic parasympathetic outflow), rostral ventrolateral medulla, including the putative homologous site of the preBötzinger complex involved in respiratory rhythm generation, vestibular nuclei (head control and hypotensive reflexes), and caudal raphé complex (cardiorespiratory integration). The types of abnormalities included gliosis enhanced by the immunomarker glial fibrillary acidic protein for reactive astrocytes, neurotransmitter deficits detected by immunocytochemistry or tissue receptor autoradiography, and apoptosis detected by relevant immunomarkers, e.g., caspase 3 [12, 72].

Reported neurotransmitter/neuromodulator defects in different brainstem sites in SIDS infants include catecholaminergic, nicotinic and muscarinic cholinergic, glutamatergic, serotonergic (5-HT), and neuropeptide systems, suggesting that no single neurotransmitter system is at fault, but that a combination of systems are most likely involved [12, 72]. Nevertheless, we found that the majority of SIDS infants show abnormalities in several markers of 5-HT function in the medulla oblongata (caudal brainstem) in regions that are critically related to state-dependent modulation of cardiorespiratory control and that are mediated by medullary 5-HT neurons, the so-called medullary 5-HT system [74–77]. These abnormalities, now detected in four independent (nonoverlapping) datasets by us, included alterations in 5-HT receptor binding, including for the 5-HT_{1A} receptor [74–77], in nuclei that contain 5-HT neurons as well as receive 5-HT projections, decreased binding to the 5-HT transporter relative to 5-HT cell density [76], increased density of 5-HT neurons [76], and 5-HT neuronal immaturity [76]. The finding of decreased 5-HT_{1A} receptors has also been reported by independent investigators in different laboratories [78, 79]. Recently, a deficit in 5-HT levels detectable by high performance liquid chromatography, and in levels of tryptophan hydroxylase (TPH2), the key biosynthetic enzyme for 5-HT, have been reported in the same SIDS medullae and in the same regions of the medullary 5-HT system that demonstrate 5-HT_{1A} receptor binding abnormalities [77]. Of note, the medullary 5-HT profile differed between infants dying of SIDS and those dying with known chronic oxygenation disorders, suggesting that chronic hypoxia does not necessarily play a major role in the pathogenesis of the impairments in the 5-HT tissue markers [74, 77]. The data now suggest that SIDS is associated with a brainstem (medullary) disorder of 5-HT deficiency rather than 5-HT over-production [77]. Thus, experimental paradigms that attempt to mimic SIDS should consider modeling a medullary 5-HT deficiency, as found in various 5-HT related knockout mice, e.g., PET1 and Lmx1b knockouts [77]. The medullary 5-HT system is involved in the modulation and integration of diverse homeostatic functions according to the level of arousal, including upper airway control, ventilation and gasping, autonomic control, thermoregulation, responses to CO_2 and O_2, arousal from sleep, and hypoxia-induced plasticity [11, 12]. Given the wide array of these homeostatic functions, sudden death in infants with 5-HT defects with all or parts of the 5-HT system may result

from a convergence of defects in protective responses to homeostatic stressors during sleep. These responses are modulated by 5-HT, probably in conjunction with other neurotransmitters and interacting (rostral) systems [11]. In SIDS cases, we propose that insufficient 5-HT levels are produced early in development, potentially as early as the first or second trimester, resulting in a compensatory increase in immature 5-HT neurons with immature (decreased) 5-HT_{1A} binding and 5-HT transporter levels. The key factor in the sequence of neurochemical events in SIDS may be impaired regulation of TPH2, with subsequent reduced 5-HT levels and increased 5-HT cell density due to impaired feedback inhibition of 5-HT levels upon 5-HT cell number [80]. The partial, rather than total defect in 5-HT markers could help explain why medullary 5-HT-mediated pathways function reasonably well at baseline or during waking, but are unable to respond to homeostatic stressors during the sleep period when the partial deficit is unmasked in some unknown but important way by sleep itself, thereby resulting in sudden death.

Cerebellar Findings in SIDS Infants and the Central Cardiorespiratory Hypothesis

The cerebellum is a focus of active neuropathologic research in SIDS due to its recognized role in central cardiorespiratory control, particularly as it relates to vestibular reflexes and head position in the prone versus supine sleep position and positional influences upon blood pressure regulation. Maldevelopment or acquired lesions of the cerebellum, for example, could lead to an uncompensated action to recover blood pressure loss during hypotensive challenges, and would similarly be unable to restrain excessive sympathetic outflow, thereby enhancing the potential for arrhythmia, as well as to lead to inadequate head positioning during sleep (see above). The neuropathologic evidence for cerebellar involvement in SIDS include reports of: 1) increase in apoptosis with (albeit not specific to) vestibular nuclei [81] that project via vestibulo-cerebellar pathways to mediate the influences of the vestibular system upon respiration, blood pressure regulation, and head position during sleep; 2) delayed maturation of the external granular layer which contains precursor cells of the internal granular layer that migrate inward up to the end of the first postnatal year, i.e., the time frame of SIDS, and receive mossy fibers from many incoming brainstem and spinal cord systems [10, 82] an underpopulation of neurons, reflected in decreased density, in neurons within the inferior olive which provide the sole source of climbing fibers to the cerebellum [83]; and delayed myelination in cerebellar-related pathways in the context of generalized hypomyelination in several brainstem and forebrain sites [84]. How these different acquired and developmental processes inter-relate to produce potential cerebellar dysfunction in SIDS is uncertain. Also uncertain are the mechanisms leading to dysfunctional processes. The well-recognized susceptibility of the human fetal and infant cerebellum to hypoxia-ischemia suggests this insult plays a role [83]. Impaired action of 5-HT projections to the cerebellum and/or inferior olive (cerebellar-relay) from abnormalities in the medullary 5-HT system, particularly the caudal raphé complex, is likely to contribute to altered motor responsiveness to compromised airways. Further neuropathologic research into cerebellar-brainstem interconnecting pathways in SIDS infants is needed.

Developmental-Dependent Neural Organization in Central Cardiorespiratory Control

A defining characteristic of SIDS is a developmental period of high risk, with relative protection in the first postnatal month and in the second six months. It is thus useful to examine central time sequences of responses to chemoreceptor and blood pressure stimuli, and thus determine what structures may place an infant at risk. As one example, the deep cerebellar nuclei play a role in CO_2 regulation [40], and help mediate compensation for extremes in blood pressure loss or excessive sympathetic outflow. The latter role is age-dependent in animals, and may be similarly subject to developmental processes in infants. Animal functional magnetic resonance imaging studies suggest that cerebellar structures serve essential roles for regulating blood pressure very early in life, but that a transition

occurs, with more-rostral brain structures assuming a greater role with development [85]. Similarly, ventral medullary surface activity, measured with optical procedures, increases to pressor challenges in young felines, but that activity reverses after day 24 [86]. Substantial reorganization of brainstem neurotransmitter systems takes place shortly after the 12th day of life in the rat, with several of those systems playing significant roles in metabolism, breathing, baroreceptor gain, and blood pressure [87–90]. Since infants are relatively protected from SIDS in early life [1], some neural developmental process likely underlies the failure process. An analogous pattern of neural regulatory mechanisms in autonomic and respiratory control may be operating in humans as shown in rodent models. Substantial evidence exists that prenatal exposure to nicotine, alcohol, cocaine or heroin alters developmental processes which significantly increase the risk for SIDS [11, 12]; the best documented is nicotine exposure with risk factors of 1.9 [91]. Such a remarkable increase in risk could only result from significant interference with vital cardiac or breathing systems. The systemic interference likely results from an interaction of nicotine with 5-HT neurotransmitter components, such as the demonstration of reduced 5-HT receptor binding following prenatal nicotine exposure [80, 92]. In addition to effects of nicotine exposure, evidence exists that low maternal hematocrit values are linked to enhanced SIDS risk [93].

CONCLUSIONS

The available evidence suggests that multiple neural mechanisms contribute to the fatal lethal event in SIDS. The processes may develop from a range of otherwise seemingly-innocuous circumstances, such as external airway obstruction or accidental extreme flexion of the head of an already-compromised structure of the infant upper airway. The fatal event may occur during rapid eye movement sleep, which imposes a paralysis of muscles necessary to restore airway patency or activate reflexes or motor activity to overcome a profound loss of blood pressure. Neural processes that could overcome those transient events with reflexive compensation appear to be impaired in SIDS. The evidence ranges from subtle physiological signs that appear very early in life, to autopsy findings of altered neurotransmitter systems that have extensive roles in breathing, cardiovascular regulation, and thermal control. Cardiovascular and respiratory systems are closely integrated to support vital functions, and it is useful to consider interdependencies between these functions rather than exclusive roles for either system. The vast extent of medullary 5-HT influences on vital physiologic functions in particular suggests a significant potential for that system to contribute to the failing mechanism, likely in conjunction with other neurotransmitter systems and neuroanatomic sites, e.g., cerebellum. The determination of the fundamental basis of SIDS is critical to provide biologic plausibility to SIDS risk reduction messages so that they are closely followed. More importantly, the determination of the biologic basis of the mechanisms of failure in SIDS is essential if we are to develop *specific* diagnostic and therapeutic strategies to eradicate all SIDS deaths-the goal of all SIDS research.

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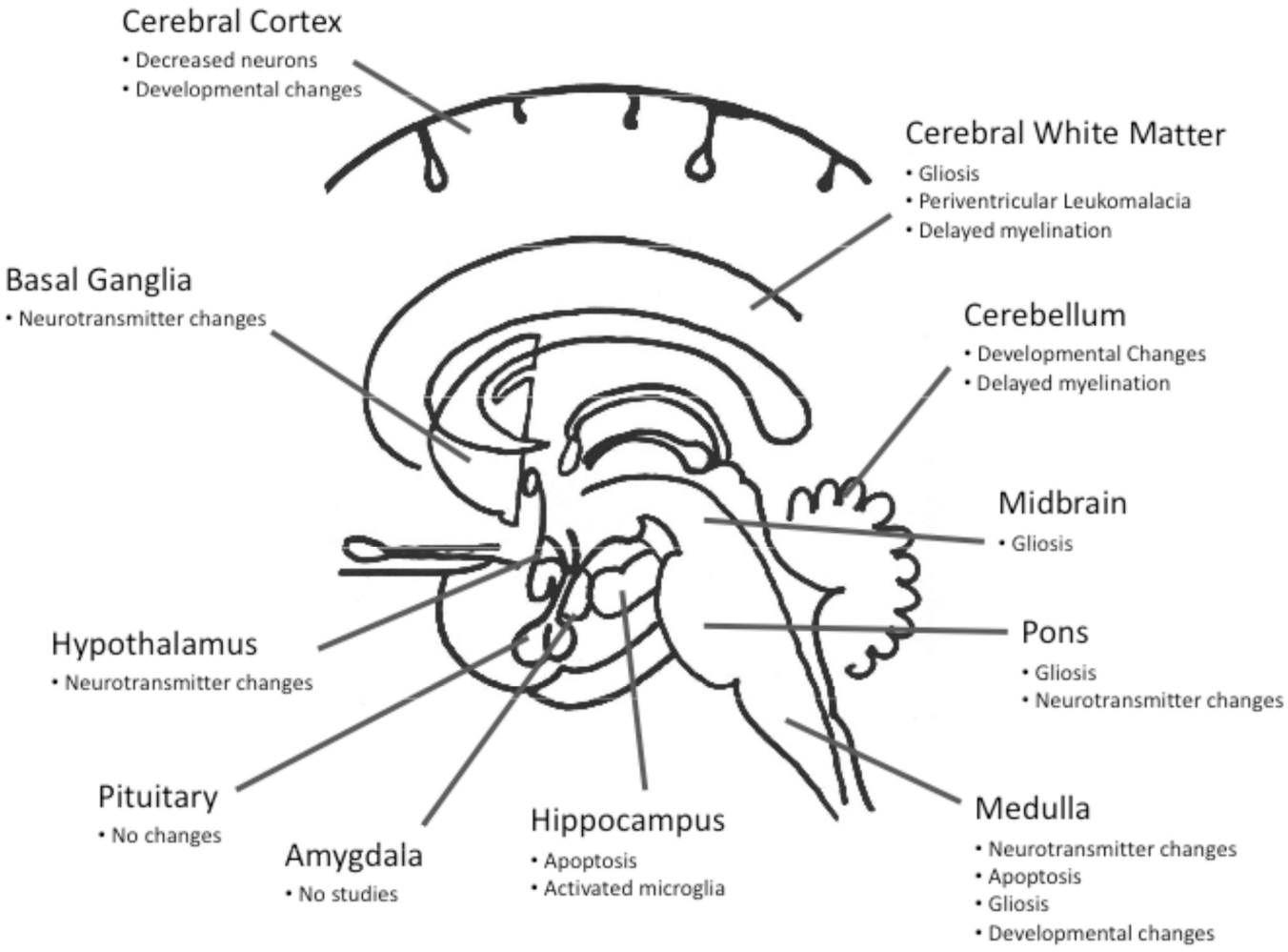

Fig. (1).
Brain regions and abnormalities in SIDS in one or more published reports. See text for references.

Table 1

Potential Mechanisms of State-Dependent Failure in Cardiovascular and Respiratory Control, Alone or in Combination, in SIDS

Cardiovascular Mechanisms	
	Bradycardia
	Hypotension (shock-like episode)
	Centrally-induced or -modulated arrythmia
	Adverse postural influences upon blood pressure control
Respiratory Mechanisms	
	External upper airway obstruction Impaired motor control of the head in the prone sleep position
	Obstructive apnea
	Central apnea
	Impaired gasping
Arousal Mechanisms	
	Impaired state-related modulation of cardiorespiratory reflexes
	Failure to arouse in response to life-threatening challenge