The role of medullary serotonin (5-HT) neurons in respiratory control: contributions to eupneic ventilation, CO₂ chemoreception, and thermoregulation

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Hodges MR, Richerson GB. The role of medullary serotonin (5-HT) neurons in respiratory control: contributions to eupneic ventilation, CO₂ chemoreception, and thermoregulation. J Appl Physiol 108: 1425–1432, 2010. First published February 4, 2010; doi:10.1152/japplphysiol.01270.2009.—The functional roles of the medullary raphé, and specifically 5-HT neurons, are not well understood. It has previously been stated that the role of 5-HT has been so difficult to understand, because “it is implicated in virtually everything, but responsible for nothing” (Cowan PJ. Foreword. In: Serotonin and Sleep: Molecular, Functional and Clinical Aspects, edited by Monti JM, Prandi-Perumal SR, Jacobs BL, Nutt DJ. Switzerland: Birkhäuser, 2008). Are 5-HT neurons important, and can we assign a general, or even specific, function to them given their diffuse projections? Recent data obtained from transgenic animals and other model systems indicate that the 5-HT system is not expendable, particularly during postnatal development, and likely plays specific roles in vital functions such as respiratory and thermoregulatory control. We recently provided a detailed and updated review of one specific function of 5-HT neurons, as central respiratory chemoreceptors contributing to the brain’s ability to detect changes in pH/CO₂ and stimulate adjustments to ventilation accordingly (9). Here, we turn our focus to recent data demonstrating that 5-HT neurons provide an essential excitatory drive to the respiratory network. We then further discuss their role in the CO₂ chemoreflex, as well as other homeostatic functions that are closely related to ventilatory control. Last, we provide additional hypotheses/concepts that are worthy of further study, and how 5-HT neurons may be involved in human disease.

RAPHÉ 5-HT NEURONS AND EUPNEIC VENTILATION

Studies aiming to elucidate the role of 5-HT in the control of breathing have resulted in mixed results, leading to conflicting conclusions that 5-HT is inhibitory, excitatory, or plays little or no role (reviewed in 25, 50). Here we discuss the data obtained from various knockout mouse models (see below) and other relevant data that provide support for the hypothesized roles of 5-HT neurons in the control of breathing, including eupneic ventilation and CO₂ chemoreception, and discuss a conceptual view of the integration of the various functions of the 5-HT system.

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as para-chlorophenylalanine (PCPA; 44). This led to an increase in respiratory output and the conclusion that 5-HT neurons inhibit breathing. However, it is now known that depletion of brain 5-HT to 10% of control has no effect on the postsynaptic response to stimulation of 5-HT fibers (7), probably due to decreased inhibition of autoreceptors on 5-HT terminals and enhanced efficacy of 5-HT release. Thus, although PCPA markedly reduces total brain 5-HT levels, it appears that there can be a compensatory increase in synaptic vesicle release mechanisms to maintain a normal level of 5-HT release (6). Alternatively, or simultaneously, a reduction in cytosolic 5-HT levels in 5-HT neurons could lead to a decrease in somatodendritic 5-HT release (which may depend more on nonvesicular mechanisms). This would lead to a decrease in 5-HT\textsubscript{1A} receptor-dependent autoinhibition and greater release of SP and TRH, and both have powerful effects on respiratory output (18, 47, 68). Thus a decrease in 5-HT synthesis may actually cause a paradoxical increase in postsynaptic stimulation by 5-HT neurons.

Confusing results have also been obtained using focal stimulation experiments. Stimulation of some parts of the medullary raphé causes an increase in respiratory output, whereas stimulation in other parts causes inhibition of breathing (31). Although it is not clear that all these effects are due to stimulation of 5-HT neurons, these results have been interpreted as indicating that some 5-HT neurons have direct excitatory connections with the respiratory network whereas others have direct inhibitory connections. However, direct inhibitory connections have never been demonstrated. Instead, it is well known that there are recurrent collaterals between 5-HT neurons (63, 64), and increasing 5-HT suppresses 5-HT neuron activity (1), and as a result breathing could be inhibited when one group of 5-HT neurons is stimulated because they inhibit other 5-HT neurons that stimulate breathing. Thus data obtained during experiments manipulating the 5-HT system in vivo can sometimes be very difficult to interpret, because of these types of complexities in an intact system.

There are two bodies of work that led to the unequivocal conclusion that 5-HT neurons stimulate breathing, at least in neonates. First, experiments like those from Ptak et al. (49) using the in vitro neonatal brain slice demonstrate that there are direct excitatory connections from 5-HT neurons to many of the primary respiratory nuclei, and these are essential for rhythm generation (46, 49). Second, recent in vivo experiments show that genetic elimination of 5-HT neurons in knockout (KO) mice (as opposed to elimination of 5-HT itself) severely disrupts eupneic respiratory rhythm and leads to high postnatal mortality in neonates (27). Although deletion of 5-HT neurons does not decrease eupneic ventilation in adult mammals (26), we believe that much of the existing evidence is still consistent with the concept that 5-HT neurons play an exclusively excitatory role at all postnatal ages (see below). Although there are data that have been interpreted as disproving that possibility, we believe that there are alternative interpretations of those data.

**MECHANISMS BY WHICH 5-HT NEURONS PROVIDE TONIC, EXCITATORY DRIVE TO THE RESPIRATORY NETWORK**

There is expression of multiple receptors for 5-HT, SP, and TRH on respiratory neurons, and known projections from 5-HT neurons to multiple sites within the respiratory network (8, 55, 62). Recent functional data are consistent with a strong excitatory influence on the network and reveal some of the mechanisms by which 5-HT, SP, and TRH act to facilitate eupneic breathing. With the exception of 5-HT\textsubscript{3} receptors, all 5-HT, SP [via neurokinin (NK)-1, -2, and -3] and TRH (1 and 2) receptors are G protein-coupled receptors (25). Activation of these receptors modifies the excitability of their target neurons through G protein-dependent second messengers, which alter the properties of ion channels to affect membrane excitability, in some cases without direct effects on membrane potential. This neuromodulation can increase or decrease membrane excitability, depending on the receptors being activated.

Recent in vitro experiments have specifically addressed how 5-HT neurons modulate components of the respiratory network. Ptak et al. (49) found that most raphé obscurus 5-HT neurons fire spontaneously in rhythmically active slice preparations, and these 5-HT neurons send axonal projections directly to both the pre-Bötzingher complex (pre-BötC) and hypoglossal motor nucleus, and they colocalize 5-HT and SP. In addition, many of these neurons also receive reciprocal excitatory connections from the respiratory network, with firing rate increasing during the inspiratory phase of the respiratory cycle (49). Moreover, cross-correlation analysis in vivo suggests there are synaptic connections from some raphé neurons (that were not identified as serotonergic) to respiratory neurons within the ventral and pontine respiratory groups (43). Thus these neurons are not peripheral to the respiratory network but are embedded within it.

Not only are 5-HT neurons anatomically and functionally embedded within the respiratory network, but release of 5-HT and SP is required for generation of inspiratory motor output in rhythmically active slices (46, 47, 49, 59) and in the perfused brain stem-spinal cord (in situ) preparation (27, 49). Blockade of 5-HT receptors, alone or in combination with NK-1 receptors, eliminates respiratory motor output in neonatal slices and neonatal and juvenile perfused preparations (27, 49). In addition, an increase in firing rate of raphé 5-HT neurons induced by local α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor activation is followed by an increase in burst frequency in rhythmically active slices and in situ, and the augmented respiratory burst frequency can be blocked with antagonists of 5-HT (methysergide, ketanserin, or MDL-11,939) and/or NK-1 (SR 140333) receptors (Fig. 1; Ref. 49). Finally, local application of artificial cerebrospinal fluid with 0 mM K\textsuperscript{+} into the raphé obscurus eliminated both 5-HT neuron firing and network activity, consistent with the concept that respiratory motor output in the neonatal slice is dependent on tonic 5-HT neuron firing under baseline conditions (49).

Data obtained by Toppin et al. (58) using the in situ perfused brain preparation suggests that blocking 5-HT receptors with ketanserin or methysergide has little effect on inspiratory motor output, defined as either “eupnea” or “gasping”. However, these data contrast with the findings of others using the same preparation. For example, Ptak et al. (49) showed that both hypoglossal and phrenic nerve motor outflows were completely dependent on endogenous activation of 5-HT and/or NK-1 receptors. The differences in the Ptak study from the Toppin study (58) included 1) the use of the highly selective antagonists MDL 11,939 (5-HT\textsubscript{2A} antagonist) and SR 140333 (NK-1 antagonist) instead of ketanserin and methysergide (less selective 5-HT antagonists); 2) the finding that combined block of 5-HT and NK1 receptors is more...
effective than either one alone; and 3) the Toppin study reported a large decrease in amplitude of phrenic output (>50%) with 30–40 μM methysergide, but used lower doses for the main experiments. It is not clear how effectively drugs have access to the brain interstitial space in the perfused juvenile rat brain, so higher doses may have been necessary for effective blockade.

The mechanisms of the effect of 5-HT neuron activity on respiratory outputs have begun to be elucidated. For example, hypoglossal motor neurons depolarize in response to activation of 5-HT2 (6, 15), NK-1, and TRH receptors, and this is due in part to inhibition of TWIK-related acid-sensitive K+ (TASK) channels (57). In intrinsic and nonintrinsic bursting pre-BötC neurons, 5-HT2A and NK1 receptor activation causes depolarization through modulation of cation leak conductances (49). Interestingly, these may not clear whether data from in vitro preparations are relevant to the influence of 5-HT neurons in the intact respiratory network in vivo. We now turn our attention to transgenic mouse models to provide further insights and potentially validate the hypothesis that 5-HT neurons provide tonic, excitatory drive to breathe in vivo. The strategy of these mouse models is to create dysfunction in either a component of 5-HT neuron function (transporter, receptor, key synthetic enzyme), or by varying degrees of 5-HT neuron loss, and determine the consequences on physiological control mechanisms. While these transgenic lines carry drawbacks, such as compensation due to loss of function from early in development, they have also provided important insight into the function of the 5-HT system.

One such model is derived from the genetic deletion of the “E-twenty six” (ETS) transcription factor Pet-1, which is uniquely expressed in 5-HT neurons. Pet-1 null mice retain only 20–30% of the normal complement of central 5-HT neurons, and demonstrate anxiety-like behavior (19), poor maternal care (33), and aggression (19), and an unstable breathing pattern (54). Thus Pet-1 KO mice show disrupted eupneic breathing pattern (14). The younger mice also have altered autoresuscitation responses to acute anoxia, with delays in onset of gasping and reestablishment of eupnea. Surprisingly, the number and “quality” of gasps is unaffected (54), despite the evidence that gasping is dependent on 5-HT signaling (59). Thus Pet-1 KO mice show disrupted eupneic breathing patterns and autoresuscitory responses as neonates, which improve with age.

To generate mice with more complete loss of 5-HT neurons, an alternative conditional knockout strategy was employed. LoxP sites were inserted such that they flank exons 4–6 of LIM homeobox transcription factor 1B (Lmx1b) gene. These
“floxed” Lmx1b (Lmx1b<sup>f/f</sup>) animals were then mated to mice in which the gene for cre-recombinase was inserted downstream of the enhancer region for Pet-1 (69), giving rise to Lmx1b<sup>f/f</sup> mice. Thus Lmx1b would only be deleted in 5-HT neurons of Pet-1 cre-expressing mice. These Lmx1b<sup>f/f</sup> mice have complete (>99%) and specific loss of central 5-HT neurons and severely reduced levels of CNS 5-HT (<50 pg/mg in KO mice compared with ~500 pg/mg wet tissue weight in the WT mice, and what was detected was likely due to contamination by peripheral blood 5-HT) and undetectable levels of 5-hydroxyindolacetic acid (5-HIAA) in the KO mice compared with ~350 pg/mg wet tissue weight in the WT mice (69). This occurs without any major anatomic malformations of the brain, and without any detectable change in other monoamine systems. Lmx1b<sup>f/f</sup> mice can live to adulthood, and as adults have normal breathing at rest, with the exception of reduced ventilatory frequency measured when ambient temperature is near the thermoneutral zone (26). Measurements of minute ventilation (V<sub>E</sub>), frequency, and the ratio of ventilation to oxygen consumption (V<sub>E</sub>/V<sub>O</sub>2; an index of the ability of ventilation to keep up with metabolic demand) are decreased when ambient temperature is ~25°C, in part due to a decreased core temperature (24). Thus baseline ventilation is relatively normal in adult Lmx1b<sup>f/f</sup> mice, suggesting that 5-HT neurons are not essential for breathing (although see below). In contrast, during the postnatal period there is severe hypoventilation and frequent apnea in Lmx1b<sup>f/f</sup> mice (27). For the first 2 wk of life, Lmx1b<sup>f/f</sup> mice have severe and frequent apnea, with some apneas lasting 35–55 s (Fig. 2A). When apnea was defined as a respiratory pause > 1 s in duration, 2-day-old (P2) Lmx1b<sup>f/f</sup> mice have ~7 apneas/min. When apneas were defined as longer than 5 s, they occur >50 times/h and are present in 100% of animals studied. By summing apnea durations and dividing by the length of time each animal was studied, it was found that P2 Lmx1b<sup>f/f</sup> mice typically spend 30–40% of the time apneic.

Lmx1b<sup>f/f</sup> mice have slower growth rate and higher estimated mortality (~23%) than wild-type (WT) mice during early neonatal life (27). In addition, growth rate in Lmx1b<sup>f/f</sup> mice increases and exceeds that of WT mice at the age at which apneas resolve. Since hypoxia can cause growth retardation (39), it is likely that the low growth rate in Lmx1b<sup>f/f</sup> mice is due to the severe disruption of eupneic ventilation, as the augmented growth rate after the second postnatal week coincides with loss of apnea. However, ventilation and the V<sub>E</sub>/V<sub>O</sub>2 ratio remained decreased beyond P28, indicating that improve-

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**Fig. 2.** Mice lacking 5-HT neurons display severe apnea in early development. A: raw traces of baseline ventilation in wild-type (WT; top trace) and Lmx1b<sup>f/f</sup> mice (middle trace) at 4 days of age. Note the long apnea in the Lmx1b<sup>f/f</sup> mouse. Apneas are eliminated after intraperitoneal injection of the 5-HT<sub>2A</sub> agonist 2,5-dimethoxy-iodoamphetamine (DOI; bottom trace). B: schematic of the isolated brain stem-spinal cord (en bloc) preparation, showing raw and integrated inspiratory motor output from the XII and cervical (C) nerve roots. C: XII motor output is reduced in en bloc preparations from postnatal day 2 (P2) Lmx1b<sup>f/f</sup> mice under control conditions (left) but is restored to the level of WT preparations by bath application of DOI or substance P (SP). [Adapted from Hodges et al. (27) with permission from the Society for Neuroscience.]
ment in eupneic ventilation continues well beyond the age at which apneas disappear.

5-HT plays a role as a trophic factor and is a key contributor to cortical network development (61). Thus the abnormal breathing in neonatal Lmx1b−/− mice could be due to disrupted network formation during development. This possibility was tested by measurements of respiratory motor output from hypoglossal and cervical spinal nerve roots in isolated brain stem-spinal cord (en bloc) preparations from P2 mice (27). WT preparations displayed regular and frequent bursts simultaneously in the hypoglossal and cervical nerve roots under control conditions (Fig. 2). Under these same conditions, Lmx1b−/− preparations had severely depressed burst generation, in many cases failing to burst for minutes. However, regular and frequent bursting was elicited by the 5-HT2A receptor-specific agonist 2,5-dimethoxy-iodoamphetamine (DOI), SP (alone or in combination with DOI), or 5-HT. Since respiratory output could be normalized by simply replacing the missing neuromodulators, the problem is not due to altered network formation during development (i.e., not due to a lack of trophic influences). It also suggests that although 5-HT might cross from the periphery to the CNS due to a “leaky” blood-brain barrier during embryonic development (13), baseline ventilation is not being supported by 5-HT receptor stimulation from peripheral 5-HT in early postnatal life. Thus respiratory output is likely abnormal in vivo due to a lack of neuromodulatory drive—a conclusion that is supported by the finding that systemic treatment of P2 Lmx1b−/− pups with DOI stimulates breathing rate and volume and decreases apnea (Fig. 2).

These in vivo and in vitro data demonstrate that 5-HT neurons provide the neonatal respiratory network with tonic drive that is essential for generation of respiratory output. The normalization of breathing with age can be interpreted in two ways. One possibility is that breathing is only dependent on input from 5-HT neurons in immature animals. Another possibility is that breathing is dependent on input from 5-HT neurons at all ages, but adult Lmx1b−/− mice have compensated for the loss of 5-HT neurons using some other mechanism. Existing data do not distinguish between these possibilities. However, specific antagonists of 5-HT2A (MDL 11,939) and 5-HT2C (CH2200) receptors consistently eliminate inspiratory motor output in in situ preparations from young (P6–P8) and older (P35) rats (27, 49), suggesting that activation of these receptors is required for driving inspiratory motor output even at older ages.

THE IMPORTANCE OF 5-HT NEURONS IN THE HYPERCAPNIC VENTILATORY RESPONSE

5-HT neurons are among a limited number of neurons that are thought to be central respiratory chemoreceptors (9, 50, 51). We have previously defined a respiratory chemoreceptor as a cell that possesses an intrinsic ability to respond to physiologically relevant changes in PCO2 (or pH), and consequently drives the appropriate adjustment of ventilation (51). As summarized in previous reviews (9, 25, 50, 51), evidence in support of the hypothesis that 5-HT neurons fit this definition is substantial and continues to build. The evidence that 5-HT neurons are central respiratory chemoreceptors includes 1) their anatomic location near penetrating arteries would allow them to faithfully monitor blood PCO2; 2) those on the ventral surface of the medulla overlap the location of the classically described rostral and caudal “chemosensitive zones” (5); 3) their large and intrinsic pH/CO2 sensitivity in primary cell culture and brain stem slices in vitro (52, 53, 65, 67); 4) their increased activity during hypercapnia in vivo (17, 32, 48, 60); 5) the decreased ventilatory response to hypercapnia in vivo after nonselective lesions of the raphe (23) or 5-HT neuron-specific neurotoxins (40, 42) or genetic deletion of 5-HT neurons (20, 24, 26); 6) injection of the carbonic anhydrase inhibitor acetazolamide into the raphe creates a local acidosis, and stimulates ventilation in anesthetized rats (4); 7) reverse microdialysis of high-CO2 solutions within the medullary raphe at single sites (21, 41) or at multiple sites (22) increases ventilation in anesthetized rats and goats in vivo; and 8) postnatal development of pH/CO2 sensitivity of 5-HT neurons occurs in parallel with the hypercapnic ventilatory response in vivo (11, 52, 56, 66, 67).

Male Pet-1 KO mice (which lack 70% of 5-HT neurons) have a decreased ventilatory response to hypercapnia as adults, while females do not (20). Neither male nor female Pet-1 KO mice display abnormalities in resting ventilation, or the hypoxic ventilatory response as adults. Likewise, knockout of the 5-HT transporter (SERT) also blunts the hypercapnic ventilatory response (34). SERT KO males have a 68% reduction of the hypercapnic ventilatory response, while females have a 22% reduction (34). Interestingly, SERT KO mice are characterized by increased extracellular 5-HT concentrations in the brain, which has been shown to decrease both 5-HT neuron activity (via autoinhibition) and to decrease 5-HT1A receptor binding (16, 37). It is not clear how this would influence the response of 5-HT neurons to hypercapnia, but the increase in autoinhibition has the potential to blunt the response of these neurons to a pH stimulus. Together these findings further support a role for 5-HT neurons in the CO2 chemoreflex.

In Lmx1b−/− mice the hypoxic ventilatory response is normal in the thermoneutral temperature range and only modestly reduced in cooler conditions (24, 26). Importantly, the hypercapnic ventilatory response is reduced by 50% under both conditions, irrespective of ambient or core temperature, and both male and female Lmx1b−/− mice are equally affected. Intracerebroventricular (ICV) infusion of 5-HT in Lmx1b−/− mice augments both baseline ventilation and the hypercapnic ventilatory response, essentially restoring the latter to near control levels (26). This effect on the hypercapnic ventilatory response could occur via enhancement of network excitability in response to chemoreceptor input, such as by potentiating the response to input from peripheral chemoreceptors (43). Alternatively, the increased extracellular 5-HT could enhance chemosensitivity of nonserotonergic chemoreceptors, such as those proposed to exist in the retrotrapezoid nucleus or the NTS. The decrease in the CO2 chemoreflex in these knockout models is consistent with the hypothesis that 5-HT neurons are central respiratory chemoreceptors, but the restoration of the CO2 chemoreflex by exogenous 5-HT indicates that there are mechanisms beyond intrinsic chemosensitivity by which 5-HT neurons enhance chemoreception. Thus 5-HT neurons may act both as sensors of pH themselves and as facilitators of chemoreception by other groups of neurons. Data from a variety of approaches support the proposed role of 5-HT neurons as central chemoreceptors, and the consistent and specific deficit in the hypercapnic ventilatory response in transgenic models.
reinforces the concept that 5-HT neurons play a major role in the CO₂ chemoreflex in vivo.

THERMOREGULATION AND TRANSGENIC MODELS OF 5-HT SYSTEM DYSFUNCTION

Interestingly, in addition to altered CO₂ chemoreception, each of the genetic mouse models discussed above also displays differing degrees of thermoregulatory dysfunction, consistent with the hypothesized role of raphe (5-HT) neurons as a critical relay point for descending hypothalamic drive to heat generation mechanisms (38). When these deficits are considered in combination, they provide a striking parallel with the deficiencies thought to contribute to sudden infant death syndrome (SIDS) (30, 45), which is itself characterized by multiple abnormalities in the 5-HT system. Thus it is relevant to discuss the observations of altered thermoregulation along with the known effects of 5-HT system dysfunction on ventilatory control.

Pet-1 KO, SERT KO, tryptophan hydroxylase 2 (TPH2) KO, and Lmx1bf/f/p mice all maintain appropriate core temperatures under normal conditions, but not in response to a thermal stress. Even the mild thermal stress of a convective air current at a temperature of 24–25°C is sufficient to decrease core temperature in Lmx1bf/f/p mice by ~1.5°C (24). Decreasing the environmental temperature to 4°C typically decreases core temperature in WT mice by 0.5–1.5°C, and they can maintain this temperature for days (29). In contrast, Pet-1 KO mice decrease core temperature on average by 3.5°C over 4 h in response to the same challenge (unpublished observations), similar to the temperature drop reported in SERT KO mice under the same conditions (35). In response to the same challenge, core temperature in Lmx1bf/f/p mice precipitously drops more than 6°C in 1 h, and they have to be physically removed from the cold environment and actively heated or body temperature will continue to drop to below 26°C (26). Further analysis of the dysfunction in Lmx1bf/f/p mice clearly indicates attenuation of heat generation mechanisms, including reduced shivering and a failure to sustain nonshivering (brown adipose tissue) thermogenesis during cold exposure. However, there is a normal peripheral vasoconstrictor response to cold, in addition to providing tonic, excitatory drive to breathe, 5-HT neurons provide an arousal (28, 30). In addition, multiple defects in the 5-HT regulatory dysfunction and is thought to include defects in thermoregulatory defense. These observations suggest that in addition to providing tonic, excitatory drive to breathe, 5-HT neurons provide an arousal stimulus in response to hypercapnia (due to hypoventilation or hyperventilation or apnea) during sleep. A key component of this concept is further characterizing the targets and biophysical mechanisms by which 5-HT neurons can modify postsynaptic excitation at various sites. Based on the data collected to date we continue to favor an integrative role of 5-HT neurons in homeostatic control mechanisms, through intrinsic properties and/or synaptic interactions that contribute to regulation of ventilation relative to metabolic and thermoregulatory demands.

SIDS has long been associated with breathing and thermoregulatory dysfunction and is thought to include defects in arousal (28, 30). In addition, multiple defects in the 5-HT system have now been characterized in postmortem brain tissue from SIDS cases, including decreased 5-HT₁₆ receptor binding and SERT density, and increased numbers of morphologically distinct (possibly immature) 5-HT neurons (45). Although they do not “model” SIDS, the transgenic mouse models studied to date provide important insight into how a deficit in the 5-HT system could lead to death. They point strongly to specific roles for 5-HT neurons in respiratory and thermoregulatory control, with a large contribution to CO₂ chemoreception. Further studies are required to increase our
understanding of the fundamental roles of 5-HT in homeostatic regulatory systems, and how these defects could precipitate death in SIDS.

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**DISCLOSURES**

No conflicts of interest are declared by the authors.

**REFERENCES**


