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Take a Deep Breath and Wake Up: The Protean Role of Serotonin in Preventing Sudden Death in Infancy

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Abstract

Recordings from infants who died suddenly and unexpectedly demonstrate the occurrence of recurring apneas, ineffective gasping, and finally, failure to restore eupnea and arouse prior to death. Immunohistochemical and autoradiographic data demonstrate a constellation of serotonergic defects in the caudal raphe nuclei in infants who died of Sudden Infant Death Syndrome (SIDS). The purpose of this review is to synthesize what is known about adaptive responses of the infant to severely hypoxic conditions, which unleash a flood of neuromodulators that inhibit cardiorespiratory function, thermogenesis, and arousal and the emerging role of serotonin, which combats this cardiorespiratory inhibition to foster autoresuscitation, eupnea, and arousal to ensure survival following an hypoxic episode. The laryngeal and carotid body chemoreflexes are potent in newborns and infants, and both reflexes can induce apnea and bradycardia, which may be adaptive initially, but must be terminated if an infant is to survive. Serotonin has a unique ability to touch on each of the processes that may be required to recover from hypoxic reflex apnea: gasping, the restoration of heart rate and blood pressure, termination of apneas and, eventually, stimulation of eupnea and arousal are all modulated by serotonin. Recurrent apneic events, bradycardia, ineffective gasping and a failure to terminate apneas and restore eupnea are observed in animals harboring defects in the caudal serotonergic system models – all of these phenotypes are reminiscent of and compatible with the cardiorespiratory recordings made in infants who subsequently died of SIDS. The caudal serotonergic system provides an organized, multi-pronged defense against reflex cardiorespiratory inhibition and the hypoxia that accompanies prolonged apnea, bradycardia and hypotension, and any deficiency of caudal serotonergic function will increase the propensity for sudden unexplained infant death.

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1 Introduction

Sudden Infant Death Syndrome (SIDS) and asphyxial deaths represent the single largest causes of deaths in infancy (age 1–12 months) (2016). Occasionally, whether by design or by accident, the events leading up to the deaths of infants attributed to SIDS have been recorded with a variety of accompanying physiological data. The data among a diverse set of studies and recording methods are consistent: before death, these infants experience a series of apneas and associated bradycardias from which they initially recover, albeit sometimes only partially, until they succumb to final a period of severe apnea and bradycardia when gasping fails to restore heart rate and eupnea (Meny et al., 1994; Poets et al., 1999; Poets et al., 1993; Sridhar et al., 2003) (Fig. 1). Therefore, any hypothesis about the pathogenesis of SIDS must explain the two key features of these recordings before death: the origin of the apneas and the failure of recovery from these apneas. We believe that the designation Sudden Unexpected Infant Death (SUID), which includes SIDS, asphyxial deaths, and other poorly defined causes of death in infants less than one year of age, better captures the population of infants at risk for prolonged apneas, failed gasping, and a failure to restore eupnea and arouse that may lead to the death of an infant (Carlin and Moon, 2017; Hunt et al., 2015). Therefore, we have been pursuing studies to understand how the risk factors for SUID (and the risk factors for SIDS and asphyxial deaths within SUID are remarkably similar) either promote reflex apneas, regardless of sleep position, or inhibit or suppress effective gasping, restoration of eupnea and arousal after apneas (Leiter and Böhm, 2007).

Reflex apnea: The gateway to SUID

The main focus of this review is the multifaceted role of 5-HT in the processes that prevent or shorten prolonged apneas and promote gasping, restoration of eupnea, and arousal. However, the control of apnea initiation and duration intersects with the serotonergic system in the brainstem, and so a discussion of the putative origin of apneas in the context of SUID is a necessary prologue to further discussion of the important and protean actions of 5-HT in babies responding to hypoxic reflex apnea during sleep.

Fetal Responses to hypoxia

Apnea is elicited by hypoxia in young animals when a ventilatory response to hypoxia cannot be sustained (Mortola, 2004). The physiological adjustments to conserve oxygen as part of the response to hypoxia are best understood as a spectrum of adaptations appropriate to each particular environment and developmental state as animals pass from fetal life to adulthood.

The apneic response to hypoxia originates *in utero* where a ventilatory response to hypoxia provides no benefit; the fetus is completely dependent on oxygen delivery from uterine blood flow and its own conservative reflex responses to hypoxia. When neonatal animals are

first exposed to hypoxia, minute ventilation may increase, a response that originates from the carotid body (Blanco et al., 1984) (Bureau et al., 1985). The large surface area to body mass ratio of small or young animals makes the maintenance of body temperature energetically costly, and a hyperventilatory response to hypoxia sufficient to maintain oxygen delivery to support a constant body temperature is prohibitively expensive energetically (Mortola, 1996). Thus, for many neonatal mammals, including humans (Cross and Oppe, 1952; Cross and Warner, 1951), a hyperventilatory response to hypoxia cannot be maintained, and ventilation declines as an oxygen conserving strategy (Bissonnette, 2000). Moreover, thermogenesis is blunted in the neonate and body temperature falls (i.e. hypoxic hypometabolism (Mortola, 1999, 2004)). Oxygen consumption in infants is correlated with the availability of oxygen - the neonate behaves like a 'regulated oxygen conformer,' and part of the response to hypoxia in neonates is inhibition of metabolism (Asakura et al., 1990; Mortola, 2004). Breathing is also inhibited, sometimes to the point of apnea. If primary hypoxic apnea develops, bradycardia, redistribution of blood flow, reduced thermoregulation, and depressed cerebral oxygen consumption ensue to provide a comprehensive and integrated mechanism of oxygen conservation (all of which recapitulate the fetal response to hypoxia). The persistence of a hypometabolic response, while initially adaptive, may compromise the re-establishment of normal cardiovascular function and body temperature control between apneic events. The repetitive, incomplete recoveries of heart rate and breathing evident in physiological records from babies who died of SIDS may reflect incomplete recovery of central cardiorespiratory and thermoregulatory control between apneic events (Meny et al., 1994; Poets et al., 1999; Poets et al., 1993; Sridhar et al., 2003).

Since the work of J.D. Wood in the 1960s, it has also been realized that a flood of GABA (Wood et al., 1968), possibly involving reduced GABA reuptake (Hagberg et al., 1985), contributes directly to inhibitory neuromodulation in the hypoxic mammalian brain. Increased GABAergic drive specifically within respiratory circuits contributes to hypoxic respiratory depression (Melton et al., 1990). Adenosine is also released in abundance during severe hypoxia and, acting through excitatory A_{2A} receptors, may activate GABAergic neurons (Abu-Shaweesh, 2007; Mayer et al., 2006; Wilson et al., 2004; Zaidi et al., 2006). Adenosine, acting through adenosine A1 receptors, inhibits excitatory neurotransmitter systems (Cunha, 2001) and may permit prolonged apneas by decreasing CO_2 sensitivity (James et al., 2018). Thus, adenosine and GABA inhibit neuronal activity and cause profound suppression of cerebral metabolic activity. We believe that the reduction in cerebral metabolism, like the centrally-mediated inhibition of respiration and thermogenesis (Bissonnette, 2000; Mortola, 2004), is a controlled and regulated process that enhances survival and is neuroprotective under severe hypoxic conditions (Hochachka, 1986). Hypoxia suppresses active sleep (AS) in the fetus (a REM-like state with a relatively high cerebral metabolic rate), and the suppression of cerebral metabolism in the fetus, neonates and infants generates a state analogous to NREM sleep in adults (though infants lack the cortical maturity to manifest the EEG characteristics of NREM sleep). The analogy is apt, however, in that NREM sleep is the sleep state associated with the lowest metabolic rate, and hypothermic responses to hypoxic stress are likely entered through NREM sleep in adult animals as well (Berger, 1975; Berger and Phillips, 1993; Heller, 1988). Moreover,

adenosine is a sleep-promoting substance that fosters the appearance of slow-wave sleep (Radulovacki, 1985; Strecker et al., 2000). NREM and REM sleep are associated with active suppression of sensory afferent information; NREM REM sleep isolate the brain from outside stimuli and disruptions. In the same way, the structured, hypometabolic brain state caused by hypoxia during prolonged apneas actively isolates the infants from external stimuli. This may be one reason infants in the midst of prolonged hypoxic apneas fail to respond to resuscitation efforts, even when resuscitation is started promptly after the apneic and bradycardic events are first observed (Meny et al., 1994; Poets et al., 1999).

How do apneic responses leading to hypoxia begin?

Many investigators have recognized that the dive reflex, primary hypoxic apnea, and the laryngeal chemoreflex (LCR) have features in common with the events recorded in infants who died of SIDS. All three reflexes may be associated with apnea and bradycardia, redistribution of blood flow to vital organs, and often suppression of consciousness depending on the severity and duration of hypoxia accompanying the apnea (Li et al., 2018). These reflex apneas are also much more potent in young, immature animals and small mammals. Each of these reflexes has been thought to contribute to SIDS (Downing and Lee, 1975; Guntheroth and Kawabori, 1975; Kovar et al., 1979; Lanier et al., 1983; Page and Jeffery, 1998; Perkett and Vaughan, 1982; Thach, 1997; Wolf, 1966). The dive reflex is elicited by circumstances that seem far removed from SIDS, but primary hypoxic apnea and the LCR seem like strong candidates to initiate a process that may end in sudden death if apnea terminating and eupnea restoring processes are ineffective (Li et al., 2018).

The LCR is a protective reflex elicited by water, low chloride concentration solutions, or acid in the larynx (Boggs and Bartlett, 1982; St. Hilaire et al., 2005) and consists of a complex set of behaviors, apnea (sometimes profound), swallowing, coughing, sometimes bradycardia and redistribution of blood flow to vital organs. Many investigators have proposed that the respiratory inhibition and bradycardia associated with the LCR may result in the death of infants if they are not reversed before severe hypoxemia ensues (Downing and Lee, 1975; Page and Jeffery, 2000; Thach, 2001). Apneas can only exist if eupnea is inhibited, and this digital, reflex - on or off – switch between apnea and eupnea seems to originate in the NTS (where afferent fibers from the carotid body and larynx terminate) and requires an amplification process and likely reciprocal inhibitory mechanisms so that the animal can switch rapidly between apnea and eupnea. The rapid switching is achieved within the NTS by presynaptic modulation of glutamate release by the A- and C-fiber afferents mediating reflex apneas (Doyle et al., 2002; Fawley et al., 2014; Hermes et al., 2016; Jin et al., 2004). If the LCR is a gateway to SUID, then the physiological effects of many risk factors for SUID, such as thermal stress, maternal nicotine, fetal tobacco smoke exposure and inflammation, ought to increase the sensitivity or severity of the LCR in animals; which has been confirmed in multiple studies (Xia et al., 2011, 2016; Xia et al., 2009; Xia et al., 2010). Presynaptic transient receptor potential vanilloid 1 (TRPV1) receptors, which are abundant on C-fibers in the NTS and also participate in central sensitization of pain, provide a mechanism through which many risk factors for SUID may modulate presynaptic signaling in the NTS (Xia et al., 2011, 2016). Thus, risk factors for SUID may sensitize the LCR (Li et al., 2018), analogous to central sensitization of pain

fibers, and produce reflex allodynia in infants (potentiation of the LCR by stimuli that would otherwise be innocuous) and increase the likelihood of severe apneic events leading to sudden infant death.

Parallels exist between the cellular mechanisms underlying the LCR and those underlying peripheral chemoreflex response to hypoxia. Stimulation of the LCR and the hypoxic chemoreflex may cause apnea and bradycardia, both reflexes originate from cranial nerves, and the initially processing of both reflexes occurs in the caudal NTS. In addition to sensitizing the LCR, TRPV1 activation also increases the sensitivity of the carotid body to hypoxia (Roy et al., 2018). Central apneas are more frequent in infants at risk for SIDS (Kahn et al., 1988; Kahn et al., 1992; Kato et al., 2001), and increased carotid body sensitivity increases the loop gain of the respiratory control system and therefore decreases respiratory stability (Alvaro et al., 2012; Boros and Reynolds, 1976; Khoo et al., 1991; Nakayama et al., 2003; Smith et al., 2007; Zhao et al., 2011). Thus, risk factors for SIDS that sensitize the LCR may also sensitize carotid body function and increase respiratory instability, especially during sleep when other influences that stabilize breathing are absent (Horner, 2017; Phillipson, 1978), thereby exposing infants to a greater risk of prolonged apneas and the subsequent severe hypoxia during sleep.

Apnea during sleep: Serotonin rides in wearing a white hat

The recordings from infants who died of SIDS reveal a sequence of events in which apnea was followed by ineffective gasping, failed restoration of eupnea and failed arousal (Meny et al., 1994; Poets et al., 1999; Poets et al., 1993; Sridhar et al., 2003). Most infants experience repetitive apneas during neonatal life that diminish in frequency as infants mature (Kahn et al., 1992; Kato et al., 2001). Termination of severe apneas relies on autoresuscitation (Guntheroth and Kawabori, 1975), and autoresuscitation from apneas involves gasping, termination of apnea, restoration of eupnea, and often, arousal from sleep. It is our hypothesis that in this stereotypical train of events, each step is dependent on the preceding event; the process of successful autoresuscitation starts with gasping and reversal of bradycardia. Oxygenation must improve to allow the next processes to emerge: apnea cessation and restoration of eupnea, after which arousal from sleep may occur. Serotonin contributes to each process in a way that promotes eupnea and arousal. Figure 2 shows a schematic of the processes and sequencing of recovery from hypoxic reflex apnea and the role of serotonin in each process.

Multiple abnormalities in caudal serotonergic neurons have been described in infants who died of SIDS, and the core neuropathological lesions of SIDS are found among the serotonergic neurons in the paragigantocellularis lateralis, gigantocellularis, intermediate reticular zone, caudal raphe, and arcuate nucleus (Kinney and Haynes, 2019). These neurons send projections rostrally to a variety of respiratory-related and arousal-related nuclei, and the 5-HT derived from these nuclei has important effects on each element of the autoresuscitation process whereby apneas are terminated and regular breathing is restored. Moreover, each of the elements of autoresuscitation originates in a different part of the brainstem and seems to receive serotonergic inputs from the caudal raphe that act through different sets of 5-HT receptors (Fig. 3).

Gasping requires disinhibition and serotonergic facilitation

Active inhibition originating from the pons and possibly higher brain centers inhibit respiratory circuits responsible for the generation of gasping (e.g. pre-BotC), thereby preventing gasping behavior during eupnea (Lumsden, 1923; St John et al., 1984; St John, 1985; St John and Knuth, 1981). However, there is likely a decrease in this inhibition during severe hypoxia, which permits gasping to emerge. Glycinergic mechanisms are perhaps paramount inhibiting gasping; *in situ* experiments utilizing phrenic nerve recordings have shown that, when coupled with an increase in extracellular K^+ (a situation that is known to occur naturally under anoxic conditions) and glycinergic blockade (Blank and Kirshner, 1977), the eupneic pattern of breathing switches to a gasping pattern (St. John et al., 2002). In addition to the removal of this glycinergic braking, there is an increase in both glutamatergic and serotonergic drive within the local Pre-BotC microcircuitry during hypoxia that expedites or facilitates gasping (but is perhaps is not necessary for its initiation) (Solomon, 2004). Astrocytes are an additional key source of excitatory drive during hypoxia that counteracts GABA/glycinergic inhibition – this includes the release of gasotransmitters such as H_2S as well as ATP that binds P2Y receptors within the inspiratory pre-BotC network (da Silva et al., 2017; Rajani et al., 2018).

Serotonergic facilitation of the gasp

In reduced preparations, serotonergic neurons provide excitatory drive to the Pre-BotC to facilitate gasping. For example, 5-HT, acting on 5-HT_{2A} receptors, differentially affected pacemaker neurons; cadmium-insensitive pacemaker neurons – i.e. those that rely on persistent sodium currents necessary for gasping but not eupnea – require endogenous 5-HT_{2A} receptor activation for bursting (Pena and Ramirez, 2002; St. John and Leiter, 2008; Tryba et al., 2006). Pharmacological activation of PKC blocks the effect of 5-HT_{2A} receptor antagonism on fictive respiratory activity, suggesting that PKC activation is a key step in the signaling transduction pathways leading from 5-HT_{2A} receptors to the downstream effector molecules (Pena and Ramirez, 2002). In addition to 5-HT, Substance P is also released from serotonergic neurons in the raphe obscurus, modulating background cation leak currents to increase the excitability of pre-BotC neurons (Pena and Ramirez, 2004; Ptak et al., 2009). These effects are mediated by 5-HT_{2A}, 5-HT_{2C} and NK-1 receptors. One can reasonably conclude from the above findings that during prolonged or severe hypoxia, there is a shift away from inhibition of the gasping centers (via glycinergic disinhibition) that, when combined with 5-HT_{2A} and 5-HT_{2C} activation and increased extracellular K^+, releases the constraint on the Pre-BotC and allows gasping to emerge.

The findings from slice preparations have largely been recapitulated in whole animals, but with an important caveat: the role of 5-HT is highly dependent on stage of postnatal development. For example, studies on Pet-1−/− mice lacking about two-thirds of the usual number of serotonergic neurons demonstrated that 5-HT has little role in the genesis of gasping once the animals are beyond about 2 weeks of age (Chen et al., 2013; Cummings et al., 2011; Erikson and Sposato, 2009; St. John et al., 2009). Serotonin appears to be most efficacious terminating hypoxic apnea and initiating gasping in ~P7–10 mice; Pet-1−/− mice have profoundly delayed gasping only at this age (Chen et al., 2013; Cummings et al., 2011). This is of particular relevance to SIDS because this age is arguably comparable to human

infancy (Clancy et al., 2001). The neurophysiological basis for the relatively narrow developmental window in which 5-HT facilitates gasping has not been elucidated. It is not a function of "immature" respiratory neuronal networks; in the first few days of life (postnatal day 4–5), 5-HT-deficient Pet-1−/− mice are completely normal in terms of gasping and autoresuscitation (Cummings et al., 2011). Two subsequent studies addressed whether 5-HT exerts a physiological or developmental role within gasping centers of the brainstem. Like Pet-1−/− mice, rat pups in which 5-HT neurons were chemically lesioned postnatally a few days before testing have delayed gasping and decreased survival during severely hypoxic conditions. This suggests a physiological, rather than developmental, role for serotonin as a facilitator of gasping. Perhaps more convincing evidence that serotonin exerts a physiological role comes from mice in which 5-HT neurons were acutely "silenced" using Designer Receptor Exclusively Activated by Designer Drug (DREADD) in mice. During activation of DREADD receptors, the mice demonstrated delayed and less effective gasping (Dosumu-Johnson et al., 2018). These findings strongly support an acute facilitation of the gasping by 5-HT in neonatal animals, likely through 5-HT_{2A} and 5-HT_{2C} receptors (Pena and Ramirez, 2002).

Effective autoresuscitation depends on gasping, but there is a cardiovascular component as well. During each gasp, there is a dramatic increase in heart rate that increases cardiac output and, coupled with the dramatic increase in pulmonary ventilation, helps reverse systemic hypoxia. The primary effect of carotid body stimulation is bradycardia when there are no respiratory efforts; when vagally-mediated information associated with successful respiratory efforts is present, hypoxia is associated with a tachycardia (Angell-James and Daly, 1969, 1975; Daly et al., 1979). Therefore, the tachycardia seen with each gasp is part of a coordinated reversal of the inhibitory, apneic-bradycardic response to hypoxia to an excitatory cardiorespiratory response more appropriate for air breathing. Successful autoresuscitation cannot occur if gasping and tachycardia do not improve systemic oxygenation (Guntheroth and Kawabori, 1975). In this respect, it is interesting that in 5-HT deficient mice and rats, whether they were $\text{Pet1}^{-/-}$ or rat pups treated with 5–7 DHT, a reduction in 5-HT was associated with both reduced effectiveness of gasping and a less effective reversal of the bradycardic response to hypoxia. Moreover, compared to rats replete with 5-HT, rat pups lacking 5-HT experience a more profound decrease in arterial blood pressure that compromises survival during severely hypoxic conditions. Along with reduced cardiac output, reduced blood pressure during apnea and bradycardia undoubtedly leads to brain hypoperfusion and more profound tissue hypoxia that cannot be mitigated by gasping alone (Yang and Cummings, 2013). While the mechanisms for the support of blood pressure by 5-HT have not been revealed, it may be that 5-HT facilitates the carotid body-mediated sympatho-excitation that occurs during apnea and/or hypoxia, possibly at the level of the NTS. It is clear from these animal studies that 5-HT contributes to each component of the coordinated cardiorespiratory response to severe hypoxia; i.e. conversion of apnea to gasping and the recovery of normal heart rate and blood pressure (Fig. 2).

Serotonergic inhibition of apnea

Apnea and eupnea are mutually exclusive. Activation of the LCR and primary hypoxic apnea hold the respiratory pattern generator in a post-inspiratory apneusis, which precludes

progress through the usual three phases of eupnea: inspiration, post-inspiration, and expiration. Therefore, a necessary step in the restoration of eupnea is either the waning of the apnogenic influence arising from within the NTS, or active inhibition of that apnogenic process, so that the post-inspiratory apneusis may be terminated and eupnea may be resumed. Termination of apnea during the LCR was facilitated by activation of 5-HT_3 receptor activation in the NTS (Donnelly et al., 2016). Serotonin 3 receptors are expressed on C-fibers within the superior laryngeal nerve, and they are densely expressed within the NTS where the axons of these fibers terminate in the area postrema (AP) and NTS (Barnes et al., 2009; Pratt and Bowery, 1989; Waeber et al., 1989). We speculated that the 5-HT_3 receptors were on presynaptic terminals of GABAergic neurons, which when activated, inhibit (as yet electrophysiologically unidentified) apnogenic neurons in the NTS, which are presumably glutamatergic (Czyzyk-Krzeska and Lawson, 1991; Kubin and Davies, 1995; Remmers et al., 1986). The 5-HT that interacts with the 5-HT_3 receptors in the NTS originates from the caudal raphe (mainly the raphe obscurus) (Donnelly et al., 2017). Serotonin originating from the raphe obscurus also blunts the bradycardic response to carotid body stimulation by activating 5-HT_3 receptors in the commissural nucleus of the NTS (Weissheimer and Machado, 2007). Thus, both apnea termination and the termination of the bradycardic response to hypoxic apnea are associated with activation of 5-HT_3 receptors in the NTS, and inhibition of apnea and bradycardia set the stage for a sustained, excitatory cardiorespiratory response to hypoxia and restoration of eupnea. A deficiency of either 5-HT_3 receptors in the NTS or a deficiency of activation and release of 5-HT from caudal raphe neurons could be associated with prolonged and difficult to reverse apneas and bradycardia, and SUID may be associated with a hyposerotonergic state associated with or derived from numerous neuropathological abnormalities in the caudal raphe of babies who died of SIDS (Kinney and Haynes, 2019). Moreover, intermittent hypoxia administered to pregnant rat dams resulted in sensitization of the LCR, reduced ability of 5-HT to shorten the LCR (which as noted above depends on 5-HT_3 receptors), and a marked reduction in 5-HT_3 receptor binding in the rat pups at the same postnatal age when the LCR was prolonged (cite paper in this journal).

Thus, prenatal hypoxia appears to alter brain development in a way that sensitizes apnogenic reflexes, like the LCR, and reduces the capacity of 5-HT, which originates at least in part from the caudal raphe, to shorten and terminate reflex apnea. There are no similar studies of regulation of apnea duration following primary hypoxic apnea, but given the convergence of apnea control processes within the NTS, an effect of 5-HT_3 receptor activation on the duration of primary hypoxic apnea seems plausible. In summary, serotonergic mechanisms exist within the caudal raphe and NTS that may terminate reflex apneas and clear the way for restoration of eupnea. Should any of these processes be deficient, as we believe they are in SUID, apneas will be more difficult to terminate, and eupnea and arousal, the essential process to protect infants against prolonged hypoxic apneas, will be more difficult to initiate and maintain (Fig. 2).

Serotonergic support of eupnea

In general, 5-HT has a stabilizing effect on respiration (Lalley, 1994; Richter et al., 2003), although activation of the 5-HT_{1A} receptor can inhibit elements of the respiratory controller

(Lalley et al., 1997; Lalley et al., 1994). This stabilizing effect is most clearly seen in animals in which 5-HT is deficient. In *Lmx1b*$^{f/f/p}$ mice, which lack serotoninergic neurons, younger animals had repeated, long spontaneous apneas. When these animals were treated with 5-HT or 5-HT agonists, the respiratory pattern was regularized and the frequency of breaths increased. This serotonergic effect was achieved through 5-HT$_{2A}$ and/or neurokinin 1 (NK-1) receptors, presumably in the ventral medullary regions controlling the respiratory pattern (Hodges et al., 2009). The stabilizing effect of 5-HT on neonatal breathing has also been demonstrated in neonatal Pet-1$^{-/-}$ mice (Cummings et al., 2010) and tryptophan hydroxylase 2-deficient rat pups (Kaplan et al., 2016; Young et al., 2017). The latter specifically lack 5-HT, retaining other co-released neuromodulators like substance P and thyrotropin releasing factor that have excitatory effects on breathing. In reduced preparations, 5-HT, arising from the caudal raphe, also acts to increase respiratory frequency and stabilize breathing by stimulation 5-HT$_{2A/2C}$, 5-HT$_4$, substance P and/or NK-1 receptors in the respiratory network (Ptak et al., 2009).

Other aspects of serotonergic activity coordinate the regular transition between inspiration and expiration, and through these processes reduce the occurrence or duration of apnea. For example, 5-HT signaling through 5-HT$_{1A}$ receptors inhibits the Kolliker Fuse (KF) nucleus, a region in the dorsolateral pons that facilitates the transition from inspiration to expiration (Dutschmann and Dick, 2012). Disinhibition of the KF after blockade of inhibitory 5-HT$_{1A}$ receptors increased the frequency of apneas (Dhingra et al., 2016). In addition to stimulating eupnea, 5-HT facilitates regular cycling between inspiration and expiration, which is essential for the restoration of eupnea following hypoxic apnea.

It is beyond the scope of this review, but caudally projecting serotonergic neurons provide important inputs to thermogenesis (Morrison, 2016), and it may be that the serotonergic inputs to thermogenesis are important in re-establishing respiratory stability and thermal homeostasis following the hypometabolic, oxygen conforming state that occurs during hypoxic, reflex apneas in neonates and infants (Mortola, 1999, 2004). Moreover, lack of serotonin in *Lmx1b*$^{f/f/p}$ mice was associated both with apneas, respiratory instability, and reduced thermogenic capacity (Hodges et al., 2009). Carotid bodies also contribute to the regulation of thermogenesis during hypoxia, albeit mostly during the recovery phase once oxygen becomes available after the apnea has been terminated (Hemelrijk et al., 2019; Mortola, 2004). This suggests that the most immature mammals, including human infants - those that perhaps have the lowest carotid body sensitivity to hypoxia (Bissonnette, 2000), experience a more prolonged blunting of thermogenesis that persists even after cessation of the hypoxic stimulus, perhaps in keeping with the adaptive nature of the oxygen-conserving response. It is interesting that the recordings of infants who subsequently died of SIDS often demonstrate incomplete recovery of eupnea or full arousal from sleep. Hence, it appears that failure to restore thermal homeostasis, possibly as a result of deficient serotonergic function, may contribute to the lack of respiratory stability following repeated hypoxic apneic events.

Sudden infant death invariably occurs during sleep, but there is no clear indication whether SUID occurs preferentially in NREM sleep or REM sleep (analogous to AS in infants). Respiratory activity is more variable during REM or active sleep (Horner, 2017), and it seems likely that apneic and bradycardic events leading to sudden death occur

predominantly in REM or AS, which is also the sleep state associated with the least serotonergic activity. Young and colleagues asked whether the apneas displayed by neonatal serotonin-deficient rodents showed any dependency on state; i.e. were they more frequent in quiet sleep (analogous to NREM in adults) or active sleep? Compared to wild-type littermates, TPH2$^{-/-}$ pups displayed increased spontaneous apneas, specifically during prolonged periods of AS (Young et al., 2017). The increased apnea of TPH2−/− rat pups was ameliorated by central administration of atropine, suggesting that elevated cholinergic drive to respiratory centers - probably originating from the pontine tegmentum, a key "REM driver" – contributed to apneic phenotype (Davis et al., 2019). Even in normal infants and neonates, AS may be considered a "risky" state, given the destabilized respiratory, heart rate and arterial blood pressure that characterize this state (Horner, 2012; Horner, 2017). A loss of 5-HT may put an infant at greater risk for apnea and the initiation of events that may lead to SUID specifically in AS. In addition to more apnea (Kahn et al., 1988; Kahn et al., 1992; Kato et al., 2001), there is evidence that infants who subsequently died of SIDS cases had more AS than quiet sleep (Schechtman et al., 1992). Serotonergic dysfunction may have a role in both of increasing the amount of AS and decreasing respiratory stability during that stage of sleep in infants at risk for SIDS/SUID.

Serotonergic support of arousal

Arousal from sleep is associate with set of physiological responses, usually in a stereotypical sequence, including an increase in heart rate, blood pressure and muscle tone (reversing the relatively low heart rate and blood pressure and laxity of muscle tone associated with sleep), a sustained respiratory effort (though there may be a brief pause in breathing), and activation of the EEG. In human infants, arousal begins with an augmented breath (sometimes followed by a brief apnea) or a startle, increased heart rate and a change in the EEG activity reflecting the arousal (usually low voltage faster activity) (McNamara et al., 2002; McNamara et al., 1998). This stereotypical sequence has been described in piglets and rat pups and may occur spontaneously or may be elicited by exposure to hypoxia and/or hypercapnia (BuSha et al., 2001; Darnall et al., 2010; Dauger et al., 2001). Based on the timing and pattern of the events within the arousal response, the arousals in infants seem to begin with autonomic changes originating from the brainstem (respiratory and heart rate changes) and then ascend, partially or completely, to the cortex. Hence, arousals originate in the brainstem (BuSha et al., 2001; McNamara et al., 2002; McNamara et al., 1998).

SIDS is associated with serotonergic defects in the caudal raphe (Kinney and Haynes, 2019), and arousal responses appear to be inadequate in babies who died of SIDS (Harper and Bandler, 1998; Hunt, 1981; Kahn et al., 2002; McCulloch et al., 1982). Numerous studies have linked deficient serotonergic activity in the caudal raphe to failed or deficit arousal responses. Toxigenic lesion studies using 5,7-DHT, a toxin that specifically kills serotoninergic neurons, injected into the medullary raphe in P2 rat pups resulted in an 80% reduction in medullary 5-HT neurons. When these animals were studied at P5, P15, and P25, pups injected with 5,7-DHT had longer arousal latencies and a reduced respiratory frequency response to hypoxia at all three ages tested compared to control rat pups (Darnall et al., 2016). Similar results were obtained in *Pet-1*$^{-/-}$ knock-out mice, which have

dramatically reduced numbers of serotonergic neurons. Pups between the ages P6-P10 were exposed to four episodes of hypoxia during sleep.

After the onset of hypoxia, the latencies to arousal in *Pet-1*$^{-/-}$ pups were significantly longer than in wild-type control animals. The arousal latency tends to habituate (get longer) after repeated exposure to hypoxia, and arousal habituation was also greater in *Pet-1*$^{-/-}$ knock-out mice compared to wild-type control animals (Darnall et al., 2011). Moreover, TPH2$^{-/-}$ pups have delayed arousal responses to increasing CO_2 in both QS and AS, while arousal responses to hypoxia were unaffected (Young et al., 2017). Hypercapnia appears to be a more potent arousing stimulus than hypoxia (Kaur et al., 2013), as discussed below, even though both stimuli are present during hypoxic reflex apnea.

Serotonergic facilitation of arousal: central and peripheral mechanisms

As noted above, arousals seem to begin caudally and project rostrally. The cortical component of arousals are generated by an ascending arousal system that originates in the rostral pons and includes the parabrachial nucleus, which projects to the basal forebrain and then to the cortex (Fuller et al., 2011). The parabrachial nucleus integrates arousing stimuli related to hypercapnia (Kaur et al., 2013), hypoxia (Darnall, 2013), and vagally-mediated mechanoreceptor information from the airways (Kaur and Saper, 2019). Serotonergic neurons in the caudal raphe send projections to the parabrachial nucleus (Bang et al., 2012; Miller et al., 2011), where 5-HT may enhance arousals to hypercapnic stimuli by acting through 5-HT2$_A$ receptors (Buchanan and Richerson, 2010; Buchanan et al., 2015). The 5-HT mediating these arousal enhancing effects may originate in part from the raphe magnus (Darnall et al., 2016), but possibly other caudal raphe nuclei. In addition, hypoxia-sensitive neurons in the rostral ventrolateral medulla may also contribute to arousal response, though whether this depends on serotonergic mechanisms is less clear (Guyenet and Abbott, 2013). Serotonin may amplify the arousing effects of carotid body and vagal stimuli at the level of the parabrachial nucleus, but the role of amplification of hypercapnic inputs to arousal at the level of the parabrachial nucleus has been more fully elaborated (Kaur and Saper, 2019).

The foregoing survey of studies makes it clear that 5-HT originating from the caudal raphe participates in multiple processes that are important in reversing hypoxic apnea and bradycardia, but this leaves unanswered the question, what stimulates serotonergic neurons as the apnea progresses so that they can overcome the inhibition that is central to the hypometabolic apneic response to hypoxia? The simplest answer is that the duration of the apnea leads to progressive hypercapnia and hypoxia. Carotid body chemoreceptors detect hypoxia and to a lesser extent, hypercapnia and increase ventilation when activated. Central chemoreceptors detect hypercapnia, and there are oxygen sensitive neurons in the ventral medulla that may participate in the restoration of eupnea following apneas in infants (Bamford and Carroll, 1999; Carroll and Fitzgerald, 1993; Gauda et al., 2009; Guyenet and Abbott, 2013; Kholwadwala and Donnelly, 1992). Activity from the carotid bodies also contributes to behavioral arousal in response to hypoxia, and denervation of the carotid bodies reduced arousal in response to hypoxia and airway obstruction (Fewell et al., 1989; Fewell et al., 1990). The involvement of serotonergic neurons in carotid body-mediated arousal is supported by the observation that stimulation of the carotid sinus nerves induces

FOS-like protein (a marker of neuronal activation) in regions of the medullary raphe (Erickson and Millhorn, 1991). Hypercapnia appears to be a potent activator of arousal through the parabrachial nucleus, which is enhanced by serotonergic inputs (Kaur and Saper, 2019). In a similar way, the hypercapnic response generated within the retrotrapezoid nucleus (RTN) may also be amplified by serotonergic inputs. There are also projections from midline serotonergic neurons to the RTN (Brust et al., 2014; Rosin et al., 2006), and serotonergic projections from the medullary raphe to the RTN amplify the neuronal and ventilatory responses to hypercapnia originating within the RTN (Dias et al., 2008; Mulkey et al., 2007; Wu et al., 2019). The amplification of CO_2 sensitivity within the RTN depends on 5-HT_2 and 5-HT_7 receptors acting on two different ph-sensitive channels mediating CO_2 sensitivity of RTN neurons: HCN channels are modulated by 5-HT_2 receptors (Hawkins et al., 2015) and KCNQ channels were modulated by 5-HT_7 receptors (Mulkey et al., 2007). Any amplification of CO_2 sensitivity within the RTN will further enhance the arousing potential of hypercapnia, which may be further amplified by serotonergic inputs to the parabrachial nucleus discussed above. Thus, the projections from the RTN to arousal-promoting neurons in the parabrachial nucleus (Rosin et al., 2006) and carotid body afferents to the parabrachial nucleus likely concurrently stimulate ventilation and promote arousal as a dual-pronged approach to overcome the inhibition of breathing associated with hypoxic reflex apnea.

Serotonin and the risk of SUID

Serotonergic defects are common in babies who died of SIDS (Duncan et al., 2010; Paterson et al., 2006) and also in babies who died of under circumstances that were consistent with asphyxia (Randall et al., 2013). We think it is likely that even though there has been diagnostic drift (Hunt et al., 2015), deaths of infants that are labeled as asphyxial, may still reflect disorders of the serotonergic system. First, the risk factors for SUID, which reflect SIDS and asphyxial deaths, encompass many of the factors that were previously associated with SIDS and may contribute to the serotonergic defects identified in infants who died in circumstances consistent with asphyxia (Randall et al., 2013). It is our belief that deficiencies of gasping, termination of apneas due to hypoxia, restoration of eupnea and arousal are likely also deficient in infants whose deaths are labeled asphyxia. Hence, difficulty terminating apnea, restoring eupnea and arousing from sleep likely contribute to deaths in infants that were attributed to both to asphyxia and to SIDS. Based on the hypotheses presented above, the severity of serotonergic defects, whether the cause of death is listed as SIDS or as asphyxia, will dictate the extent to which infants can overcome hypoxic apneic events. In addition to the benefit of reoxygenation associated with gasping, serotonin is the primary neurotransmitter organizing the recovery from reflex apneas and hypoxia.

Summary

Surviving episodic hypoxia is essential, and neonates and infants are in a difficult transitional stage in which they do not have sufficient body mass or energy reserves to mount an effective and sustained euthermic response to hypoxia. Therefore, an oxygen conserving and hypothermic response to that permits oxygen consumption to decline during hypoxia is essential to prolong survival, but there must be a mechanism of reevaluation of

this strategy, a way to reassess, and a way to reverse the hypometabolic, apneic and bradycardic response to hypoxia. The intrinsic hypoxic sensitivity of the gasping mechanism provides this opportunity to reevaluate the hypometabolic strategy and begins the process whereby infants may re-establish eupnea. If gasping restores oxygenation, the apnea may be terminated, the cardiorespiratory response may be converted from an inhibitory pattern to an excitatory pattern and the respiratory rate and heart rate may increase, and the infant may arouse as the final step in complete restoration of a vigorous waking response to hypoxia. In our analysis, hypoxia, adenosine and GABA are part of a centrally controlled and structured pattern of responses to survive hypoxia, and oxygen and 5-HT are arrayed against these inhibitory influences to reduce the impact of adenosine (reoxygenation) and provide excitatory inputs to the key events necessary to restore normal breathing. There are surely more excitatory neurotransmitters brought into play during the recovery from apnea, but 5-HT is a major factor. Infants who died of SIDS have an array of defects that mainly involve the caudal raphe (Kinney and Haynes, 2019); it is our hypothesis that these defects compromise the ability of infants at risk for SIDS to mount an effect and timely defense against the potent evolutionary adaptations fostering apneic and hypometabolic responses to hypoxia. In summary, we believe that infants at risk for SIDS (and SUID) have both an increased propensity for apneas derived from sensitization of the LCR and/or carotid body activity, which increases the strength of the apneic, hypometabolic response to hypoxia, and defects in serotonergic function that limit the effectiveness of those behaviors that are meant to reverse hypoxia. This sequence of events, an increased frequency and/or severity of apneic events and bradycardia and a reduced capacity to generate effective gasping, terminate apneas, restore eupnea and arouse, is compatible with the cardiorespiratory recordings made in infants who subsequently died of SIDS (Kelly et al., 1986).

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1 Abbreviations go here

AS	Active sleep
GABA	gamma-amino butyric acid
LCR	laryngeal chemoreflex
NREM	non-rapid eye movement
NTS	nucleus of the solitary tract
REM	rapid eye movement
SIDS	Sudden Infant Death Syndrome
SUID	Sudden Unexpected Infant Death
TRPV	transient receptor potential vanilloid

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Highlights

- Apnea and bradycardia can be an appropriate response to hypoxia in infants when a ventilatory response cannot be maintained
- Autoresuscitation, inhibition of apnea, restoration of eupnea and arousal are essential to terminate apnea and bradycardia in infants
- Infants at risk for SIDS may have heightened sensitivity of the reflex mechanisms precipitating apneas and bradycardias
- The caudal serotonergic system supports all the processes necessary to terminate apnea and bradycardia: serotonin facilitates gasping and autoresuscitation, shortens or terminates reflex apneas, stimulates eupnea and drives arousal from the caudal brainstem rostrally to the cortex
- Each of these processes is associated with activation of a different set of serotonergic receptors in specific regions of the brainstem targeted by serotonergic neurons in the caudal raphe.

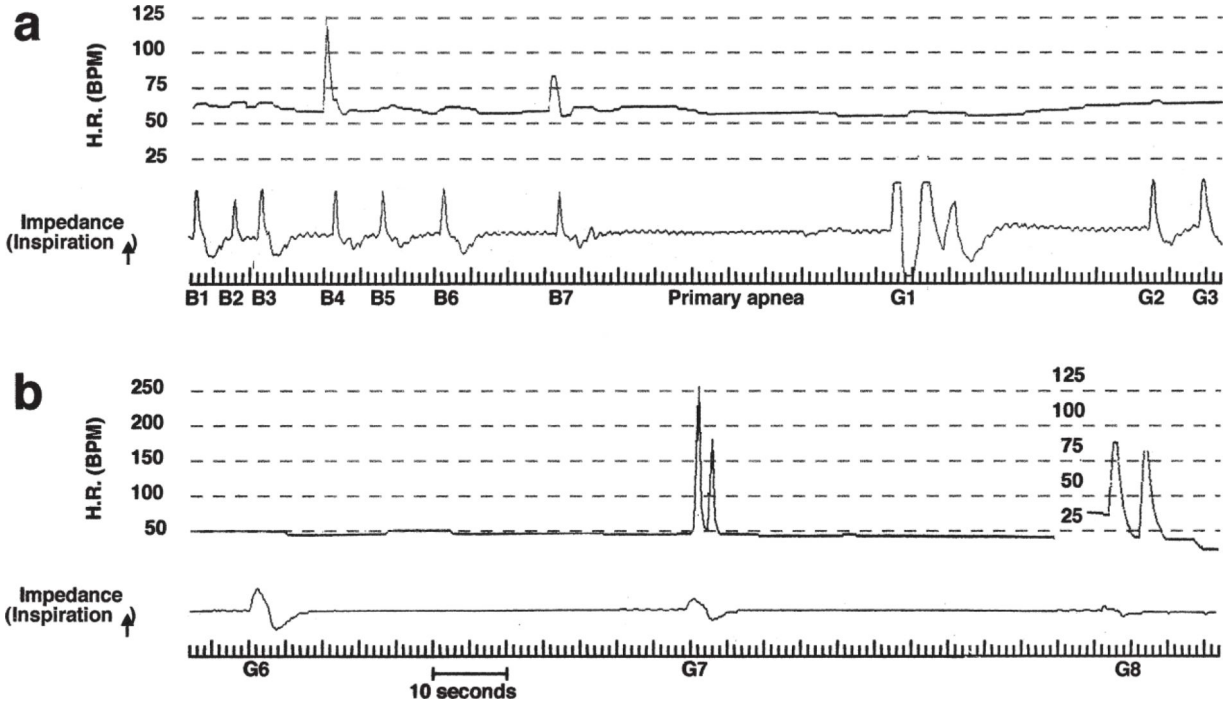

Figure 1.

Recordings of heart rate (H.R.) by ECG and respiratory activity by thoracic impedance in an infant classified as a SIDS case. (a) Breaths (B) 1 through 7 show a slowing of respiratory rate (i.e. progressively longer apnea) in a background of severe bradycardia (Normal HR = ~150 bpm). As hypoxia becomes more severe respiratory activity ceases altogether (primary hypoxic apnea). Three gasps (G1–3) then emerge, the respiratory component of "autoresuscitation". (b) Terminal gasps (6 through 8) in the same record are shown – note that gasping has not succeeded in elevating H.R. or re-establishing eupnea; i.e. failed autoresuscitation. Reproduced from Sridhar *et al.*, 2003.

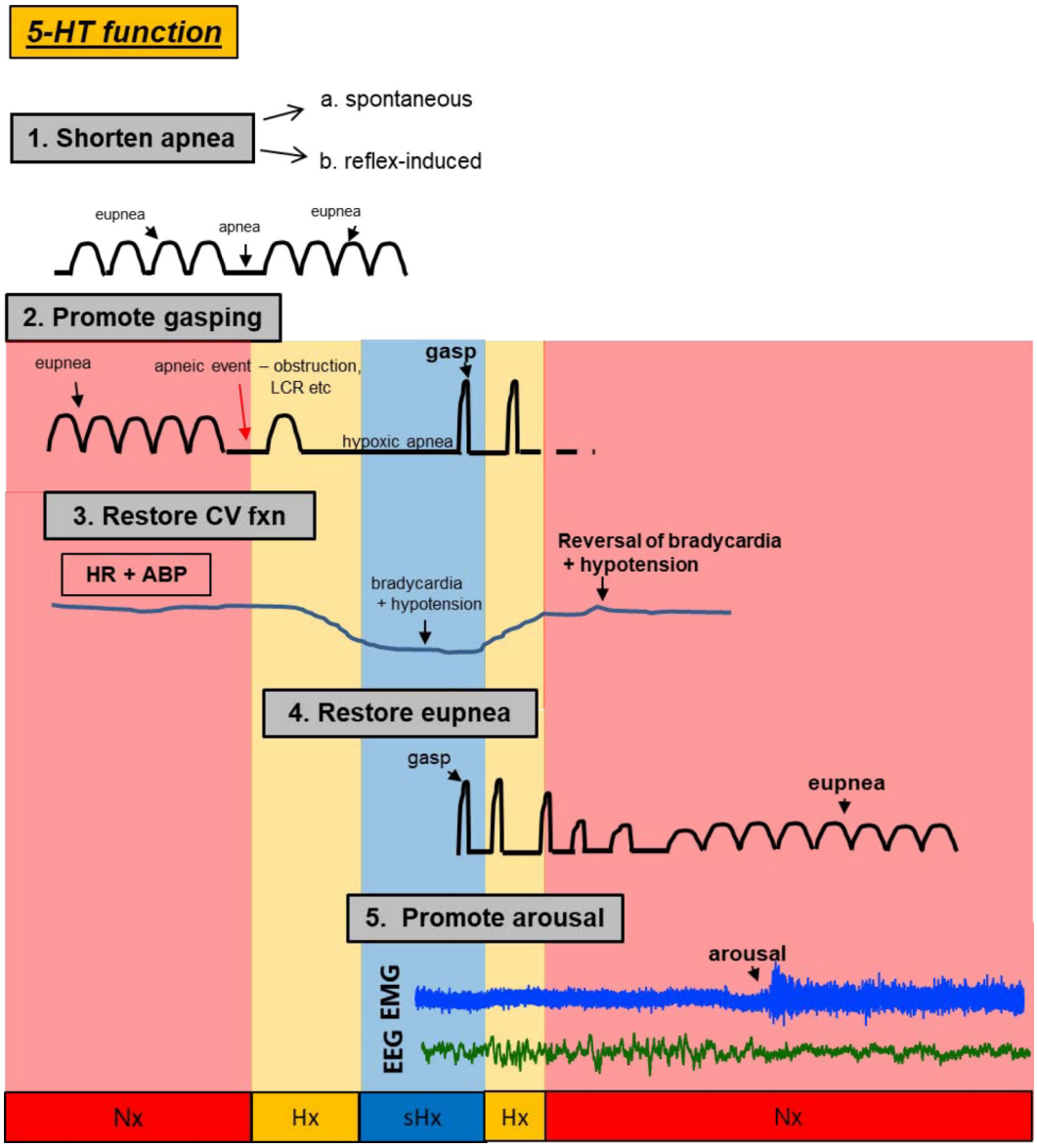

Figure 2.

The critical role of central serotonin (5-HT) on cardiorespiratory homeostasis and arousal following spontaneous, reflex- or hypoxia-induced apnea. Shown are specific functions of 5-HT on: 1. the prevention or mitigation of spontaneous (see Erickson *et al.,*2007, Hodges *et al.*, 2009, Ptak *et al.*, 2009, Cummings *et al.*, 2010, Kaplan *et al.* 2016, Young *et al.*, 2017) or reflex-induced apneas (*i.e.* those initiated by the laryngeal chemoreflex (LCR) (see Donnelly *et al.,* 2016, 2017); 2. the promotion of gasping during severe hypoxia (see Pena and Ramirez, 2002, Tribe *et al.*, 2006, Erickson and Sposato, 2009, Cummings *et al.,* 2011, Chen *et al.,* 2013, Dosumu-Johnson *et al.*, 2018), 3. the restoration of cardiovascular function during the gasping phase (see Cummings *et al.,* 2011, Chen *et al.,* 2013, Yang and Cummings, 2013, Dosumu-Johnson *et al.*, 2018), 4. the eventual restoration of eupneic breathing (see St. John and Leiter, 2007, Erickson and Sposato, 2009, Cummings *et al.,* 2011, *Chen et al.* 2013, Dosumu-Johnson *et al.,* 2018), and finally, 5. arousal (see Buchanan

and Richerson, 2010, Buchanan *et al.*, 2015, Darnall *et al.*, 2011, Darnall *et al.* 2016, Kaur *et al.,* 2013, Kaur and Saper, 2019). Gasp: high-amplitude, low frequency respiratory motor output in response to severe hypoxia; eupnea: normal breathing; apnea: no breathing; CV: cardiovascular; HR: heart rate; ABP: arterial blood pressure; EMG: electromyograph; EEG: electroencephalograph. Colored regions represent normoxic (Nx, *red*), hypoxic (Hx, *orange*), and severely hypoxic (sHx, *blue*) conditions.

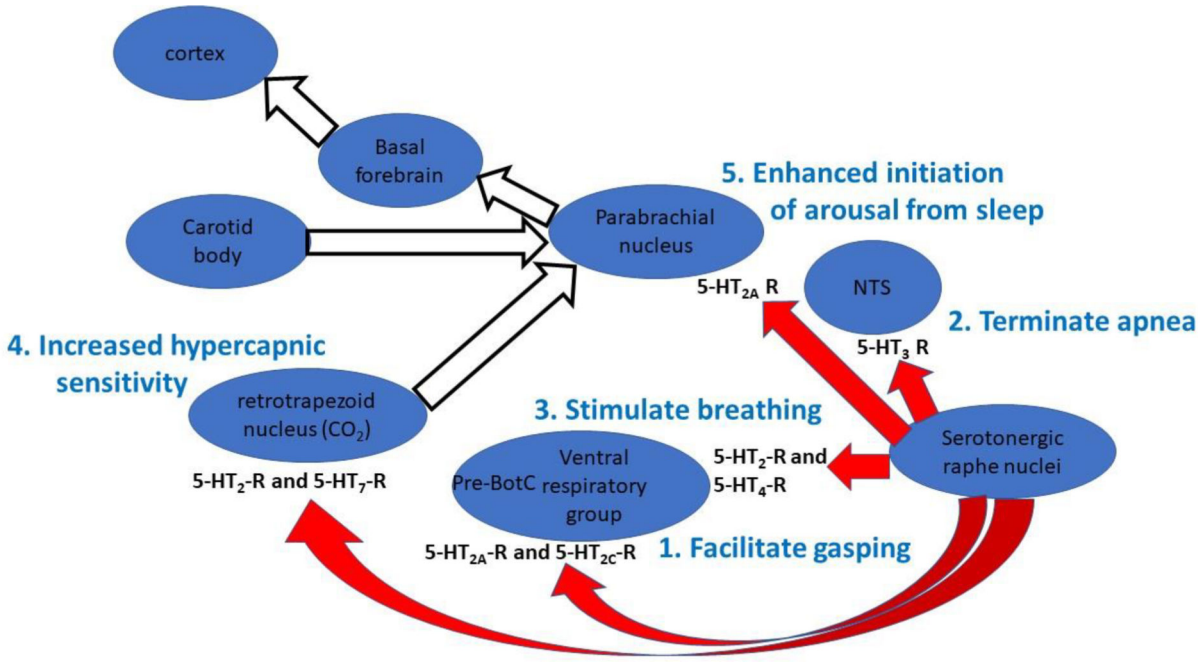

Figure 3.

The schematic representation of brainstem nuclei portrays the important role of serotonin originating from the caudal raphe interacting with different nuclei within the brainstem to organize the sequential processes that are essential to restore normal breathing following reflex, hypoxic apneas and bradycardia. Within each target nucleus, a different set of serotonin receptors seems to mediate the action of serotonin, but ultimately, the serotonergic neurons within the caudal raphe drive these processes. Moreover, the processes of recovery from hypoxic, reflex apnea seem to proceed from the caudal brainstem rostrally to the cortex through the brainstem nuclei and following the numbered sequence shown above. Autoresuscitation appears first (if the hypoxic apnea is sufficiently severe), termination of apnea follows, eupnea is restored next, and finally arousal is facilitated by enhanced hypercapnic sensitivity and amplification of arousing inputs to the parabrachial nucleus. Failure or deficiency of any one of these processes may increase the likelihood that a sleeping infant does not recovery successfully from hypoxic, reflex apnea.