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Medullary Serotonin Defects and Respiratory Dysfunction in Sudden Infant Death Syndrome

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Abstract

Sudden infant death syndrome (SIDS) is defined as the sudden and unexpected death of an infant less than 12 months of age that occurs during sleep and remains unexplained after a complete autopsy, death scene investigation, and review of the clinical history. It is the leading cause of postneonatal mortality in the developed world. The cause of SIDS is unknown, but is postulated to involve impairment of brainstem-mediated homeostatic control. Extensive evidence from animal studies indicates that serotonin (5-HT) neurons in the medulla oblongata play a role in the regulation of multiple aspects of respiratory and autonomic function. A subset of SIDS infants have several abnormalities in medullary markers of 5-HT function and genetic polymorphisms impacting the 5-HT system, informing the hypothesis that SIDS results from a defect in 5-HT brainstem-mediated control of respiratory (and autonomic) regulation. Here we review the evidence from postmortem human studies and animal studies to support this hypothesis and discuss how the pathogenesis of SIDS is likely to originate *in utero* during fetal development.

1. The Sudden Infant Death Syndrome

The sudden infant death syndrome (SIDS) is defined as the sudden death during sleep of an infant less than one year of age, that remains unexplained after a thorough investigation including performance of a complete autopsy, and review of the circumstances of death and the clinical history (Willinger et al. 1991). Despite significant reductions in SIDS rates in recent years due to successful risk-reduction campaigns, SIDS remains the leading cause of death for infants between 1 month and 1 year of age in developed countries (Mathews et al. 2002). The majority (90%) of SIDS deaths occur within the first 6 postnatal months, with the peak incidence observed at 2-4 months of age (Stewart 1975a; Stewart 1975b). Multiple studies have identified robust associations between SIDS and environmental risk factors, including prone or face down sleeping (Fleming et al. 1990; Fleming et al. 1996; Blair et al. 2006), bed sharing (Blair et al. 1999; Hauck et al. 2003; Tappin et al. 2004; Tappin et al. 2005; Pelayo et al.

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2006; Mitchell 2007; O'Mara 2007; Vennemann et al. 2009), and over-bundling (Fleming et al. 1990; Fleming et al. 1996). Several risk factors for SIDS relate to the mother and pregnancy, including prematurity, low birth weight, prenatal and postnatal cigarette smoke exposure (Schoendorf et al. 1992; Haglund 1993; Blair et al. 1996; Fleming et al. 1996; MacDorman et al. 1997; Wisborg et al. 2000; Anderson et al. 2005; Mitchell et al. 2006) and prenatal alcohol ingestion (Scragg et al. 1993; Alm et al. 1999; Iyasu et al. 2002; Kinney et al. 2003; Klug et al. 2003; Duncan et al. 2008b). There is also a male bias in SIDS with twice as many boys than girls dying of SIDS (Froggatt et al. 1968; Beal 1972; Stewart 1975b; Arneil et al. 1985; Millar et al. 1993). Likewise, there is a noted ethnic disparity with significantly increased SIDS rates among African American infants and Native American infants (Mathews et al. 2002). The Triple Risk hypothesis of SIDS has proven useful in thinking about SIDS etiology (Filiano et al. 1994). It posits that SIDS occurs when three factors impinge on the infant simultaneously– an underlying vulnerability in the infant, a critical period in development (the first 6 postnatal months when 90% of SIDS occurs), and homeostatic stressors heightening the infant's vulnerability (e.g. at the time of infant death hypercapnia from rebreathing exhaled air as a result of sleeping prone in the face-down position). While the pathogenesis of SIDS remains unknown, consensus of opinion implicates impairment of brainstem-mediated respiratory and autonomic control, including reduced chemoreceptor sensitivity (Shannon et al. 1977; Hunt et al. 1981), respiratory rhythm abnormalities (Steinschneider 1977; Kelly et al. 1979), failure to initiate inspiration (Hunt 1981; Hunt et al. 1981), and gasping deficit (Hunt 1981) leading to the infant death. Extensive evidence from animal studies indicates that brainstem serotonin (5-HT) systems influence several aspects of respiratory function (Richerson 2004; Hodges et al. 2008a). Multiple abnormalities in markers of 5-HT function are present in the brainstem of approximately 70% of SIDS infants (Paterson et al. 2006b). This observation informs the hypothesis that a defect in brainstem 5-HT networks resulting in failure of protective respiratory (and autonomic) responses to potentially life-threatening, but normally occurring sleep-related events (e.g., face down position) with sequelae including hypoxia, hypercapnia might account for SIDS in a subset of cases. In this review we discuss the evidence from human and animal studies to support the hypothesis that defective 5-HT mediated regulation of respiratory and autonomic function contributes to the SIDS death and how specific features of 5-HT neuronal function and development are synergistic with the environmental and genetic risk factors associated with SIDS.

2. Distribution of 5-HT Neurons in the Brainstem

Neurons synthesizing 5-HT (and expressing tryptophan hydroxylase [TPH]), localized exclusively to the brainstem in distinct cell groups classically defined as B1-B9, differentially project to virtually all regions of the neuraxis (Dahlstrom et al. 1964; Steinbusch 1981; Steinbusch et al. 1981; Törk et al. 1990; Jacobs et al. 1992; Hornung 2003). These cell groups are divided into a rostral domain consisting of groups B4-B9 in the midbrain and a caudal domain consisting of groups B1-B3 in the medulla (Fig 1). The two domains of the brainstem 5-HT neurons are distinct in their developmental origins, functions, and connectivity (Dahlstrom et al. 1964; Steinbusch 1981; Steinbusch et al. 1981; Törk et al. 1990; Jacobs et al. 1992; Hornung 2003). The rostral domain, located in upper brainstem, projects “rostrally” and diffusely to the cerebral cortex, thalamus, hypothalamus, basal ganglia, hippocampus, and amygdala. It participates in the mediation of arousal, cognition, mood, motor activity, and cerebral blood flow. The caudal domain in the medulla projects “caudally” and diffusely to other brainstem sites (see below), cerebellum, and spinal cord (Dahlstrom et al. 1964; Steinbusch 1981; Steinbusch et al. 1981; Törk et al. 1990; Jacobs et al. 1992; Hornung 2003) and influences breathing, cardiovascular control, autonomic output, motor control, and pain processing.

3. Medullary 5-HT Neurons and Respiratory Function

In rodents, medullary 5-HT neurons are located in the midline raphé (including, the raphé pallidus, raphé magnus and raphé obscurus) and in the parapyramidal region at the ventrolateral medullary surface. These neurons project to the nucleus of the solitary tract (NTS), nucleus ambiguus (nAm) retrotrapezoid nucleus (RTN), preBötzinger Complex (preBötC), hypoglossal motor nucleus (HG) in the brainstem, and phrenic motor nucleus in the cervical cord (Steinbusch 1981; Steinbusch et al. 1981; Holtman et al. 1986; Holtman et al. 1987; Holtman 1988; Connelly et al. 1989; Smith et al. 1989; Zhan et al. 1989; Pilowsky et al. 1990; Voss et al. 1990; Jacobs et al. 1992; Manaker et al. 1993; Feldman et al. 2003) and modulate several aspects of respiratory function including respiratory rhythmogenesis, central chemosensitivity, and long-term changes in respiratory function (i.e., respiratory plasticity).

3.1 Respiratory Rhythm Generation

Medullary 5-HT neurons play an important role in the generation and modulation of respiratory rhythmogenesis. Raphé 5-HT neurons have reciprocal connections with neurons in the preBötC (the central pattern generator) and stimulation of these neurons releases 5-HT stimulating respiratory output-effects that are blocked by 5-HT receptor antagonists (Morin et al. 1990; Morin et al. 1991a; Morin et al. 1991b; Di Pasquale et al. 1992; Al-Zubaidy et al. 1996; Ptak et al. 2002; Schwarzacher et al. 2002; Ptak et al. 2009). While 5-HT is predominantly excitatory (Hodges et al. 2008a), specific aspects of preBötC function and respiratory rhythm are mediated by specific 5-HT receptor subtypes including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{4A} receptors (Morin et al. 1990; Morin et al. 1991a; Morin et al. 1991b; Di Pasquale et al. 1992; Onimaru et al. 1998; Manzke et al. 2003; Cao et al. 2006; Gunther et al. 2006; Qin et al. 2007; Manzke et al. 2008). Evidence suggests that the 5-HT_{2A} receptor is particularly important in preBötC function and is necessary for the generation of normal respiration (Pena et al. 2002) and for gasping (Tryba et al. 2006; St-John et al. 2008).

3.2 Respiratory Chemosensitivity

Medullary 5-HT neurons, located in close proximity to large arteries entering the brainstem, are thought to detect arterial changes in PCO_2 (see Corcoran et al., 2009 this issue), thereby impacting respiratory chemosensitivity. 5-HT neurons are intrinsically chemosensitive *in vitro*, and some increase their firing rate *in vivo* in response to hypercapnia (Richerson et al. 2001; Wang et al. 2001; Bradley et al. 2002; Richerson 2004; Hodges et al. 2008b). Raphé 5-HT neurons modulate the function of chemosensitive neurons in the retrotrapezoid nucleus (RTN) (Mulkey et al. 2007; Guyenet et al. 2008) (see Guyenet et al. and Onimaru et al., this issue) and application of 5-HT receptor agonists to the classic chemoreceptor zones on the ventral medullary surface stimulates respiration in anaesthetized rats and cats (Millhorn et al. 1986; Holtman et al. 1994; Lalley et al. 1994; Lalley et al. 1995; Richter et al. 1999; Valic et al. 2008).

3.3 Respiratory Plasticity

Medullary 5-HT neurons also play a significant role in several forms of respiratory plasticity (Feldman et al. 2003) including long term facilitation (LTF) of respiration following hypoxia. Long-term facilitation is an enhancement of ventilation or respiratory motor output that persists for hours after intermittent hypoxia (Mitchell et al. 2001). Activation of 5-HT_{2A} receptors in the phrenic nerve nucleus is necessary to trigger a cascade of downstream events that ultimately result in a glutamatergic-mediated enhancement of respiratory drive to the diaphragm and accessory respiratory musculature (Baker-Herman et al. 2004; Mahamed et al. 2007; Mahamed et al. 2008). Similarly, 5-HT_{2A} receptors are necessary for the induction of LTF in the hypoglossal nucleus following episodic hypoxia and evoke a persistent increase in genioglossus and hypoglossal nerve activity (Fuller et al. 2001; McKay et al. 2005). A recent

study also suggests that 5-HT integrates cardio-respiratory responses to hypoxia as 5-HT_3 receptor antagonists inhibit respiratory-related excitation of cardio-vagal neurons in the nAm during hypoxia (Dergacheva et al. 2009).

4. Lesion of Medullary 5-HT Neurons in Animals Results in Respiratory and Autonomic Dysfunction

Animals in which medullary 5-HT neurons have been lesioned or inhibited pharmacologically display respiratory and autonomic dysfunction. Permanent lesion of medullary 5-HT neurons via injection of 5-HT neuronal toxins (Nattie et al. 2004; Penatti et al. 2006) or focal acute inhibition of 5-HT neurons by dialysis of 8-hydroxy-2-[di-*N*-propylamino]-tetralin (8-OH-DPAT) (5-HT_{1A} autoreceptor agonist) in the medullary raphé (Messier et al. 2004; Taylor et al. 2005) decreases the ventilatory response to CO_2 in newborn piglets. Transgenic mice with near complete (Lm×1b knockout) and severe (Pet-1 knockout) loss of 5-HT neurons show distinct abnormalities in breathing during early postnatal life (Erickson et al. 2003), reduced ventilatory response to CO_2 and an inability to maintain body temperature in cold stress (Hodges et al. 2008a; Hodges et al. 2008b). Notably, transgenic mice overexpressing the 5-HT_{1A} auto-receptor (which arguably have reduced extracellular 5-HT levels) die suddenly and unexpectedly in postnatal life (Audero et al. 2008). These mice exhibit spontaneous episodes of bradycardia accompanied by a drop in body temperature, with some animals dying during these episodes (Audero et al. 2008). Animal models where 5-HT is in excess also display respiratory dysfunction. Injection of neonatal rats with the 5-HT precursor L-tryptophan increases brain 5-HT level and induces potentially fatal apneas (Hilaire et al. 1993). Similarly, mice lacking monoamine oxidase (MAO), the major enzyme for 5-HT breakdown, have elevated levels of 5-HT and display an increased frequency of respiratory pauses compared to wild-type mice, defects which are resolved by pharmacological blockade of 5-HT receptors or 5-HT biosynthesis (Real et al. 2007). In addition, 5-HTT knockout mice show a dramatic decrease in the ventilatory response to CO_2 (Li et al. 2008); while mice lacking 5-HT_{2A} protein display an increased frequency of respiratory pauses during non-REM sleep (Popa et al. 2005). The observations in these animal models support the idea that altering medullary 5-HT function is detrimental to physiological control systems and may contribute to sudden unexpected death. Taken together, these data provide conclusive evidence that medullary 5-HT neurons regulate multiple aspects of respiratory function including respiratory rhythm generation and chemosensitivity, and respiratory and autonomic plasticity.

5. The Medullary 5-HT System in Humans

In humans, medullary 5-HT neurons are located in regions homologous to the 5-HT neurons in the rodent brainstem, including the midline raphé (raphé obscurus and raphé pallidus), extra-raphé (gigantocellularis [GC], paragigantocellularis lateralis [PGCL] and intermediate reticular nucleus [IRZ]), and in the arcuate nucleus (Arc) at the ventral medullary surface (Kinney et al. 2004) (Fig 2). These cell groups constitute the Medullary 5-HT System as defined by Kinney et al., (2007). Evidence from neuron tract tracing studies with the lipophilic fluorescent dye 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) indicates that these 5-HT neurons send projections to one another as well as to nuclei with respiratory-related function including the NTS and HG (Zec et al. 1997; Zec et al. 2001; Zec et al. 2003); a hypothesis supported by the presence of serotonin transporter (5-HTT), 5-HT_{1A} receptor, and 5-HT_{2A} receptor binding sites in each of these regions (Paterson et al. 2004; Paterson et al. 2006b; Paterson et al. 2009). Comparative anatomy indicates that the Arc is homologous to the respiratory chemosensitive fields at the ventral medullary surface of rodents and cats (Filiano et al. 1990; Paterson et al. 2006a). It is proposed to play a similar role in respiratory CO_2 sensitivity in humans as it expresses both 5-HT and glutamate neurons (Paterson et al. 2006a), recognized respiratory chemosensors (Mulkey et al. 2004; Richerson

2004; Weston et al. 2004). Similarly, the PGCL in the rostral ventrolateral medulla of the human is homologous to the medullary region in which the preBötC is located in rats (Kinney et al. 2007; Paterson et al. 2009). We have previously identified neurons in the PGCL that co-express immunoreactivity for neurokinin-1 (NK1) receptors, and somatostatin (SST), markers in combination for rodent preBötC neurons (Paterson et al., unpublished observations), raising the possibility that these neurons are homologues of rodent preBötC neurons and, likewise, play a role in respiratory rhythm generation. In addition, these neurons express immunoreactivity for both 5-HT_{1A} and 5-HT_{2A} receptors (Fig 3) suggesting that, as in rodents, respiratory rhythmogenesis in the human is modulated by 5-HT. These observations support the idea that 5-HT neurons in the human medulla play similar roles in the modulation of respiratory function as demonstrated for 5-HT neurons in rodents.

6. Medullary 5-HT System Abnormalities, Respiratory and Autonomic Dysregulation, and SIDS

Abnormalities in markers of 5-HT function have been observed in the medullary 5-HT system (i.e., raphé obscurus, PGCL, IRZ, Arc, HG, NTS) in SIDS infants, including an increased number of 5-HT neurons, many of which are immature (Paterson et al. 2006b), reduced 5-HT_{1A} and 5-HT_{2A} receptor expression (Panigrahy et al. 2000; Ozawa et al. 2002a; Ozawa et al. 2002b; Kinney et al. 2003; Paterson et al. 2006b), reduced 5-HTT binding (Paterson et al. 2006b), abnormal TPH expression (Sawaguchi et al. 2003; Machaalani et al. 2008), reduced brain 5-HT levels (Sparks et al. 1991), altered 5-HT turnover (Cann-Moisan et al. 1999) and altered 5-HT breakdown (Sparks et al. 1991). These observations inform the idea that multiple elements of respiratory and autonomic regulation, mediated by the 5-HT System, are defective in SIDS, including but not restricted, to respiratory rhythmogenesis and respiratory responses to hypercapnic and/or hypoxic challenge. This idea is supported by a SIDS infant who was observed to have subtle respiratory and cardiac dysfunction at birth and 5-HT receptor binding abnormalities at autopsy 2 weeks later (Kinney et al. 2005). Taken together, the above observations provide evidence to support the idea that medullary 5-HT abnormalities cause respiratory dysfunction that potentially contributes to the death of the infant in SIDS, i.e., in terms of the Triple Risk Model of SIDS, the medullary 5-HT defect is, or is part of, the underlying abnormality that predisposes the infant to sleep related death particularly when combined with an environmental stressor, such as prone sleeping, during the critical developmental period.

7. Medullary 5-HT System Abnormalities in SIDS Originate During Fetal Development

Several observations indicate that SIDS is a developmental disorder that originates during fetal life: the incidence of SIDS is greater in preterm and growth restricted infants; the peak incidence of SIDS is related to a critical and finite early developmental period (2-4 postnatal months); and prenatal exposure to environmental toxins including cigarette smoke (Schoendorf et al. 1992; Haglund 1993; Blair et al. 1996; Fleming et al. 1996; MacDorman et al. 1997; Wisborg et al. 2000; Anderson et al. 2005; Mitchell et al. 2006) and alcohol (Scragg et al. 1993; Alm et al. 1999; Iyasu et al. 2002; Kinney et al. 2003; Klug et al. 2003; Duncan et al. 2008b; Lavezzi et al. 2009) are major risk factors for SIDS. Evidence from post-mortem human studies suggests that the development of the medullary 5-HT System is abnormal in SIDS, including an increased number of 5-HT neurons with immature morphology (Paterson et al. 2006b), abnormal/immature synapse formation (Paterson et al. 2006b), and differential age-related changes in 5-HT receptor binding (i.e., binding decreases significantly with postnatal age in SIDS cases but not controls) in the medulla of SIDS cases compared to controls (Panigrahy et al. 2000; Kinney et al. 2003). These observations offer a possible explanation for the low

incidence of SIDS during the first postnatal month, followed by the period of peak incidence at 2-4 months: at birth 5-HT function is relatively normal, but becomes progressively defective during the first postnatal month as 5-HT receptor binding decreases; by 2-4 months 5-HT dysfunction reaches the "threshold" whereby the infant is unable to respond appropriately to an environmental stressor (e.g., hypoxia), ultimately leading to the sudden death of the infant.

7.1 Altering Fetal 5-HT Levels Results in Postnatal Respiratory Dysfunction in Animals

In both rodents (Gaspar et al. 2003; Nakamura et al. 2007) and humans (Kinney et al. 2007) 5-HT neurons are among the first to be expressed during embryogenesis: they develop from embryonic days 10-12 in mice and are present as early as 7 gestational weeks in humans (Kinney et al. 2007). During development 5-HT has neurotrophic actions and plays a role in regulating cell division, migration, differentiation and synaptogenesis (Lauder 1988; Lauder 1990). Thus, alterations in 5-HT levels during fetal life may adversely affect the intrauterine and postnatal development of the 5-HT and other related neuronal systems. Indeed, both depletion and elevation of 5-HT during gestation adversely affect respiratory neuronal network development and function in animals in the postnatal period. MAOA-deficient mice, who have endogenous levels of 5-HT that are 5 to 10-fold higher than wild type mice during the fetal and neonatal periods (Cases et al. 1995; Lajard et al. 1999), display abnormal expression of 5-HT_{1A} and 5-HT_{1B} receptors (Bou-Flores et al. 2000a; Bou-Flores et al. 2000b; Bras et al. 2008), abnormal phrenic nerve nucleus morphology, are unable to generate stable respiration in the postnatal period (Bou-Flores et al. 2000a; Bou-Flores et al. 2000b) and have attenuated respiratory responses to hypoxia (Burnet et al. 2001). Increasing 5-HT levels in wild type mice by pharmacological blockade of MAOA increases the number of sleep apneas (Real et al. 2007) and mice with absence of the 5-HTT protein show a dramatic decrease in the ventilatory response to CO_2 (Li et al. 2008). Similarly, transgenic mice with significant deficits in 5-HT during gestation (i.e., lm×1b and Pet-1 knockout mice) display abnormal respiratory rhythm and attenuated respiratory responses to CO_2 (Erickson et al. 2003; Hodges et al. 2008b). In addition, depletion of maternal 5-HT by injection of pregnant rats with para-chlorophenylalanine (pCPA) reduces 5-HT levels in the raphé nuclei and delays 5-HT neuronal development in the progeny (Nakajima et al. 1998; Butkevich et al. 2003).

7.2 Prenatal Exposure to Cigarette Smoke and Alcohol Adversely Affects Brainstem 5-HT System Development and Function

Exposure of the developing fetus to cigarette smoke and alcohol through the maternal circulation are major risk factors for SIDS. The mechanisms through which these toxins adversely affect the infant to predispose the baby to succumbing to SIDS are unknown, but may involve, at least partly, disruption of the developing 5-HT system as described above. Indeed, maternal cigarette smoking 3 months before or during pregnancy results in lower 5-HT receptor binding in the infant postnatally (Fig 4) (Kinney et al. 2003). In addition, a recent study identified an association between prenatal exposure to cigarette smoke and hypoplasia of the medullary 5-HT system in SIDS (Lavezzi et al. 2009). Similarly, in experimental animals, prenatal exposure to nicotine and cigarette smoke results in altered 5-HT neuron firing, 5-HT receptor expression (Kenny et al. 2001; Slotkin et al. 2006a; Slotkin et al. 2006b; Slotkin et al. 2006c; Slotkin et al. 2007b), 5-HTT expression (Muneoka et al. 2001;Xu et al. 2001; Slotkin et al. 2007a; Slotkin et al. 2007b), 5-HT turnover and depletion of brain 5-HT in the postnatal period (King et al. 1991;Muneoka et al. 1997). These adverse effects appear to result from the binding of nicotine to nicotinic and/or 5-HT receptors on 5-HT neurons (Bitner et al. 2002;Cucchiaro et al. 2003;Aznar et al. 2005). In the developing human medulla, nicotinic receptors are expressed by 5-HT neurons throughout the medullary 5-HT system, including in the raphé obscurus and arcuate nucleus (Duncan et al. 2008a), thus nicotine may act directly on medullary 5-HT neurons to alter their development and/or function. Indeed, a recent study identified that prenatal nicotine exposure abolishes 5-HT mediated activation of cardio-vagal

neurons in response to hypoxia/hypercapnia (Kamendi et al. 2009). Prenatal exposure to alcohol in the maternal circulation is also associated with reduced 5-HT receptor binding (Fig 4) (Kinney et al. 2003). In animal models of prenatal alcohol exposure, various abnormalities of the 5-HT system have been observed, including reduced 5-HT levels and reduced 5-HT receptor binding (Druse et al. 1988), retarded process outgrowth and migration of 5-HT neurons, reduced density of 5-HT fibers in the medial forebrain bundle, and reduced 5-HT neurons in the median and dorsal raphé (Sari et al. 2001;Zhou et al. 2002) and lower brainstem (Druse et al. 2004). Prenatal alcohol also adversely affects signaling molecules and transcription factors necessary for 5-HT development, e.g., sonic hedgehog which is involved in the early specification of 5-HT precursors (Ahlgren et al. 1999;Ahlgren et al. 2002), and results in defective neurogenesis, cell migration, synaptogenesis, and dendritic organization (Haydon et al. 1987;Lauder 1990;Ivgy-May et al. 1994;Mazer et al. 1997;Werner et al. 1998;Faber et al. 1999;Luo et al. 2003;Kondoh et al. 2004). Notably, the delivery of the 5-HT_{1A} agonists buspirone and ipsapirone in maternal rats prevents the alcohol-induced loss of brainstem 5-HT neurons in the pups, indicating a critical role for the 5-HT_{1A} receptor in neuronal development and alcohol neurotoxicity (Kim et al. 1996;Druse et al. 2004). These observations indicate that prenatal exposure to cigarette smoke and/or alcohol adversely affects the development and function of brainstem 5-HT systems in the postnatal period. Pre and/or perinatal exposure to these (and other toxins) may, therefore, disrupt the development of the medullary 5-HT system and account, at least in part, for the increased SIDS risk associated with maternal smoking and alcohol ingestion during pregnancy. Observations in our laboratory indicate that the human medullary 5-HT system is not fully developed at birth but continues to mature at least through the end of the first year of life (Kinney et al. 2007). This observation suggests an extended period from gestation through infancy where the medullary 5-HT system is potentially vulnerable to environmental toxins and pharmacologically active agents that may disrupt its development and function.

8. 5-HT Gene Polymorphisms and SIDS

Several studies have identified significant associations between SIDS and gene polymorphisms resulting in alterations in 5-HT neuronal function and development. These polymorphisms include two polymorphisms in the 5-HTT gene: an insertion-deletion polymorphism in the promoter region (5-HTTLPR) (Heils et al. 1997; Lesch et al. 1998) and variable number tandem repeat (VNTR) polymorphism in the second intron (Ogilvie et al. 1996; Narita et al. 2001; Weese-Mayer et al. 2003a; Weese-Mayer et al. 2003b; Maher et al. 2006; Nonnis Marzano et al. 2008; Opdal et al. 2008; Lavezzi et al. 2009), both of which are associated with increased 5-HTT expression. Similarly, a VNTR polymorphism in the promoter region of the MAOA gene resulting in increased transcription and protein expression has also recently been associated with SIDS (Filonzi et al. 2008). Individuals with these polymorphisms are postulated to have a relative reduction in synaptic 5-HT, as a result of increased 5-HT uptake and breakdown of 5-HT associated with elevated 5-HTT and MAO protein expression, respectively (Heils et al. 1997; Lesch et al. 1998; Greenberg et al. 1999; van Dyck et al. 2004). Thus, these polymorphisms may predispose an infant to increased SIDS risk by contributing to the development of, or exacerbating existing, medullary 5-HT dysfunction. Moreover, they may reduce the resilience of the infant to environmental toxins that disrupt the development and/or function of 5-HT neurons as described above. Indeed, this idea is supported by a recent study identifying an association between the LL genotype of the 5-HTT promoter polymorphism and hypoplasia in the medullary raphé and arcuate nucleus in stillborns and in SIDS cases (Lavezzi et al. 2009). Similarly, a rare mutation (IVS2 191_190insA) upstream of the third exon of the human fifth Ewing variant (FEV) gene may contribute to the development of medullary 5-HT abnormalities in a subset of SIDS (Rand et al. 2007). FEV is the human homologue of the ETS domain transcription factor Pet1 that is necessary for differentiation and development of 5-HT neurons (Hendricks et al. 1999) including regulation of TPH, 5-HTT and 5-HT_{1A} receptor gene

expression (Hendricks et al. 1999; Pfaar et al. 2002; Hendricks et al. 2003; Maurer et al. 2004; Iyo et al. 2005). Loss of the Pet1 gene in mice results in failure of approximately 70% ofl 5-HT neurons to differentiate (Hendricks et al. 1999) and deficient expression of genes required for 5-HT synthesis, uptake, and vesicular storage in the remaining 5-HT neurons (Hendricks et al. 2003). The FEV gene mutation may, therefore, result in or predispose an infant to medullary 5-HT dysfunction and, thus, SIDS. Interestingly, both the 5-HTT intron 2 gene polymorphism and the FEV gene mutation were significantly associated with SIDS in African American but not Caucasian populations (Weese-Mayer et al. 2003b; Rand et al. 2007), while the 5-HTT promoter polymorphism is present in greater frequency in Caucasian compared to African American SIDS cases (Weese-Mayer et al. 2003a). These differences among ethnic-specific gene polymorphisms/mutations may pre-dispose African American infants to greater SIDS risk than Caucasian infants and may, therefore, help explain the ethnic disparity in SIDS rates. However, despite these encouraging findings, several reports have observed no significant association between SIDS and polymorphisms in other genes pertinent to the 5-HT system, including the 5-HT_{1A} receptor (Morley et al. 2008), 5-HT_{2A} receptor, (Rand et al. 2009), and tryptophan hydroxylase 2 (Nonnis Marzano et al. 2008) genes and a polymorphism in the untranslated region downstream of the 5-HTT gene (Maher et al. 2006). These observations support the idea that the medullary 5-HT abnormalities in SIDS results from a combination of environmental and genetic factors and involves exposure of an infant with a predisposing genetic background to environmental toxins during a critical period in development, which in humans may extend from the preconceptional period through the first postnatal year.

9. Sexual Dimorphism in 5-HT Function may Predispose Male Infants to Increased SIDS risk

Twice as many male infants die of SIDS as female infants (Hoffman et al. 1992; Brooke et al. 1997; Vennemann et al. 2005). The reason for this is unknown, but identification of a significantly lower density of 5-HT_{1A} receptor binding in male compared to female SIDS infants (Fig 5) (Paterson et al. 2006b) suggests that sexual dimorphism in 5-HT function may play a role in predisposing male infants to SIDS. Indeed, significant differences in TPH, 5-HT, 5-HT metabolites, and 5-HT receptor expression, including a lower level of 5-HT_{1A} receptors, normally exist between males and females in several brain regions (Dillon et al. 1991; Arango et al. 1995; Ferrari et al. 1999; Bethea et al. 2002; Parsey et al. 2002). Interestingly, a recent study also observed that variations in the coding sequence of the 5-HT_{1A} receptor gene occur more frequently in males compared to females (Morley et al. 2008). Evidence from studies in animals with 5-HT lesions have reported male gender-specific abnormalities in respiration, chemosensitivity and thermoregulation (Penatti et al. 2006; Hodges et al. 2008b; Li et al. 2008)-responses that are modulated in part by 5-HT_{1A} receptors in the medullary raphé and extra-raphé (Messier et al. 2004; Darnall et al. 2005; Hoffman et al. 2007; Brown et al. 2008). These observations raise the possibility that male human infants may similarly have reduced sensitivity to CO_2 and temperature and that loss of medullary 5-HT_{1A} receptors, as observed in SIDS, may attenuate protective homeostatic responses to a greater extent in male compared to female infants, thus placing them at greater risk for SIDS. Evidence from animal studies also suggests reduced plasticity in 5-HT neuron function in males compared to females. Deficits in postnatal brain levels of 5-HT_{1A} receptor expression following prenatal cocaine and cigarette smoke exposure persist for a greater length of time in male compared to female rats (Johns et al. 2002; Slotkin et al. 2007a; Slotkin et al. 2007b), suggesting that the neonatal male infant brain is less resilient to exposure to at least some pharmacologically active toxins affecting 5-HT function in the maternal circulation than the neonatal female brain. Testosterone and estrogen also influence the 5-HT system and its control of respiration (Matsumoto et al. 1985; Pickett et al. 1989; Bayliss et al. 1990; Regensteiner et al. 1990; Bayliss et al. 1992;

Emery et al. 1994; Fogel et al. 2001; Liu et al. 2003; Zhou et al. 2003). Elevated levels of serum testosterone have been observed in both male and female SIDS infants compared to controls, with the highest level of testosterone observed in male SIDS infants (Emery et al. 2005). The cause(s) of elevated serum testosterone in SIDS is unknown, although prenatal exposure to nicotine increases fetal plasma testosterone in rats via inhibition of cytochrome p450 aromatase, the enzyme which converts testosterone to estradiol (Lephart et al. 2001; Stoffel-Wagner 2001). Also noteworthy is the overlap in peak SIDS incidence between 2-4 months of age and peak postnatal increase in gonadal steroids (Winter et al. 1976; Peterson et al. 1979; Forest et al. 1980). Likewise, preterm infants, a group at heightened SIDS risk, have significantly higher adrenal-derived androgens in the first year of life compared to term infants (Tapanainen et al. 1981). Thus, the normal higher levels of testosterone in male infants compared to female infants may be responsible for blunted respiratory responses to homeostatic challenges such as hypercapnia, thereby contributing to their greater SIDS risk. Taking these observations together, intrinsic differences in baseline brain 5-HT function, 5-HT neuronal plasticity, and CO_2 sensitivity between males and females provide evidence that may explain, at least in part, the greater risk of SIDS in male infants.

10. Conclusions and Remaining Questions

The data reviewed here provide evidence that the medullary 5-HT neuronal system assumes varied roles in mediating respiratory regulation and that disruption of medullary 5-HT neurotransmission by pharmacological, chemical, or genetic means produces defects in baseline respiratory and autonomic regulation as well as respiratory responses to perturbation such as hypoxic and hypercapnic challenges. These observations support the hypothesis that the medullary 5-HT abnormalities identified in SIDS cases result in respiratory and autonomic dysfunction that heightens the vulnerability of the infant. The data reviewed here also support the idea that the pathogenesis of the medullary 5-HT defect(s) in SIDS originates *in utero* and involves a combination of environmental and genetic factors. Moreover, evidence suggests that intrinsic differences in 5-HT function between males and females contribute to the increased incidence of SIDS in boys. However, the specific nature of the 5-HT dysfunction in SIDS is still unclear, i.e., is there an excess or a deficit of available 5-HT? The abnormalities in markers of 5-HT function observed in the medulla of SIDS infants may be interpreted as evidence of either 1) an increased number of 5-HT neurons leading to an excess of extracellular 5-HT and a compensatory downregulation of 5-HT receptors, or 2) 5-HT synthesis and/or release may be dysfunctional in the 5-HT neurons (which are overabundant in compensation) resulting in a deficiency of extracellular 5-HT. Indeed, both an excess and a deficit in 5-HT levels during development and in the postnatal period produce respiratory dysfunction in animal models. Determination of the level of available 5-HT in the medulla under “normal” and pathological states is therefore critical in determining the specific nature and pathogenesis of 5-HT dysfunction in SIDS. Such studies are currently underway in our laboratories. Is 5-HT the only abnormal neurotransmitter system in SIDS? It seems unlikely that this is the case. An important potential consequence of the 5-HT neuronal abnormalities in SIDS is the possibility of associated defects in GABA and substance P, known co-transmitters with 5-HT, that also regulate respiratory function. In addition, multiple other neurotransmitter systems in the medulla regulate respiratory and autonomic function in conjunction with 5-HT, including glutamate, acetylcholine, norepinephrine, somatostatin and glycine (Liu et al. 2005; Wong-Riley et al. 2005). Therefore, we propose that SIDS results from a complex interaction of multiple dysfunctional neurotransmitter systems in the brainstem of which the abnormalities in 5-HT markers are the most widely identified thus far. A systematic analysis of multiple transmitters/modulators that interface with the medullary 5-HT system is needed to establish the precise neurochemical pathology in all or subsets of SIDS cases. Without such information, the pathogenesis of the disorder cannot be established, and optimal interventions cannot be determined and implemented.

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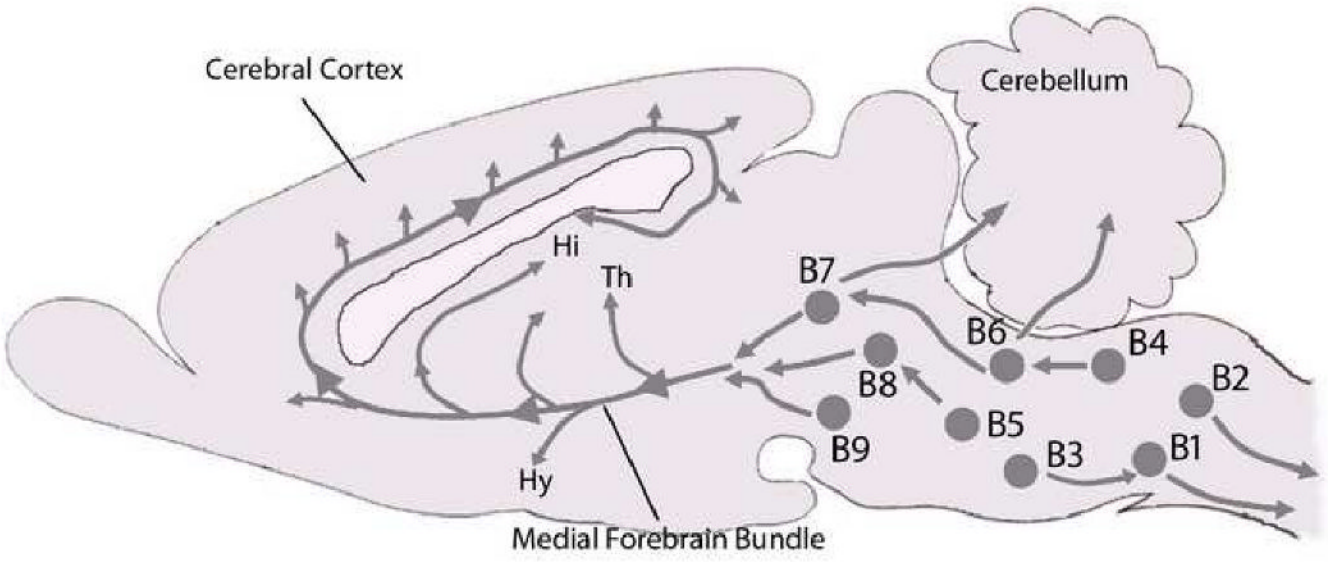

Figure 1. Distribution of 5-HT Neurons in the Brainstem

Neurons synthesizing 5-HT distribute in distinct cell groups in the brainstem classically defined as B1-B9. The rostral domain, consisting of groups B4-B9 projects "rostrally" and diffusely to the cerebral cortex, thalamus (Th), hypothalamus (Hy), basal ganglia, hippocampus (Hi), and amygdala and mediates arousal, cognition, mood, motor activity, and cerebral blood flow. The caudal domain consisting of groups B1-B3 in the medulla projects "caudally" and diffusely to other brainstem sites, cerebellum, and spinal cord and influences breathing, cardiovascular control, autonomic output, motor control, and pain processing.

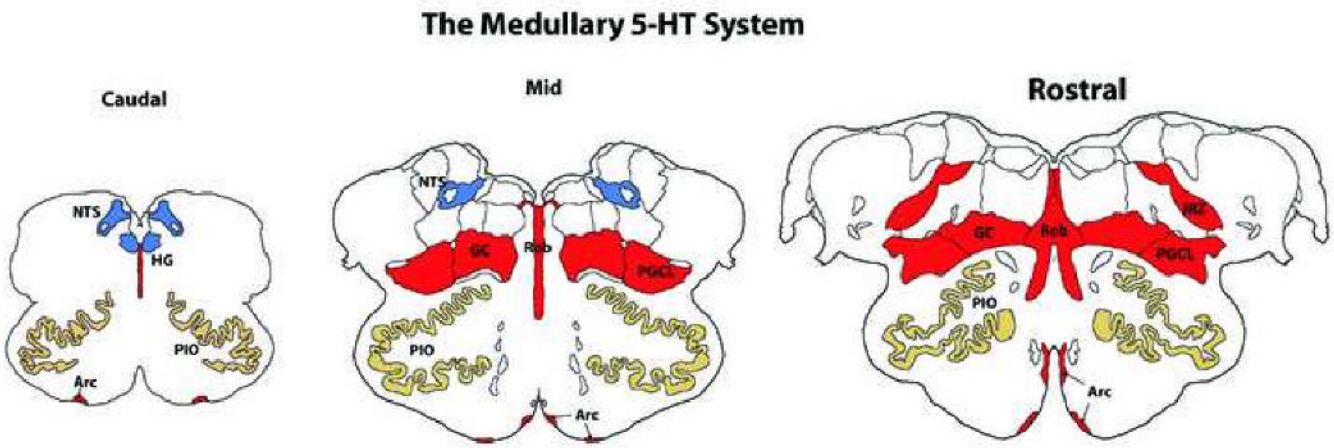

Figure 2. The Medullary 5-HT System in the Human Brainstem

The Medullary 5-HT System consists of 5-HT neurons (areas in red) in the midline raphé (i.e., raphé obscurus (Rob), extra-raphé (i.e., (gigantocellularis [GC], paragigantocellularis lateralis [PGCL], intermediate reticular nucleus [IRZ], and at the ventral medullary surface (arcuate nucleus [Arc]) and sites to which they project (blue areas) that do not contain 5-HT neurons but mediate homeostatic functions (e.g., hypoglossal nucleus [HG], nucleus of the solitary tract [NTS]). Figure shows coronal sections at the level of the Caudal, Mid, and Rostral medulla.

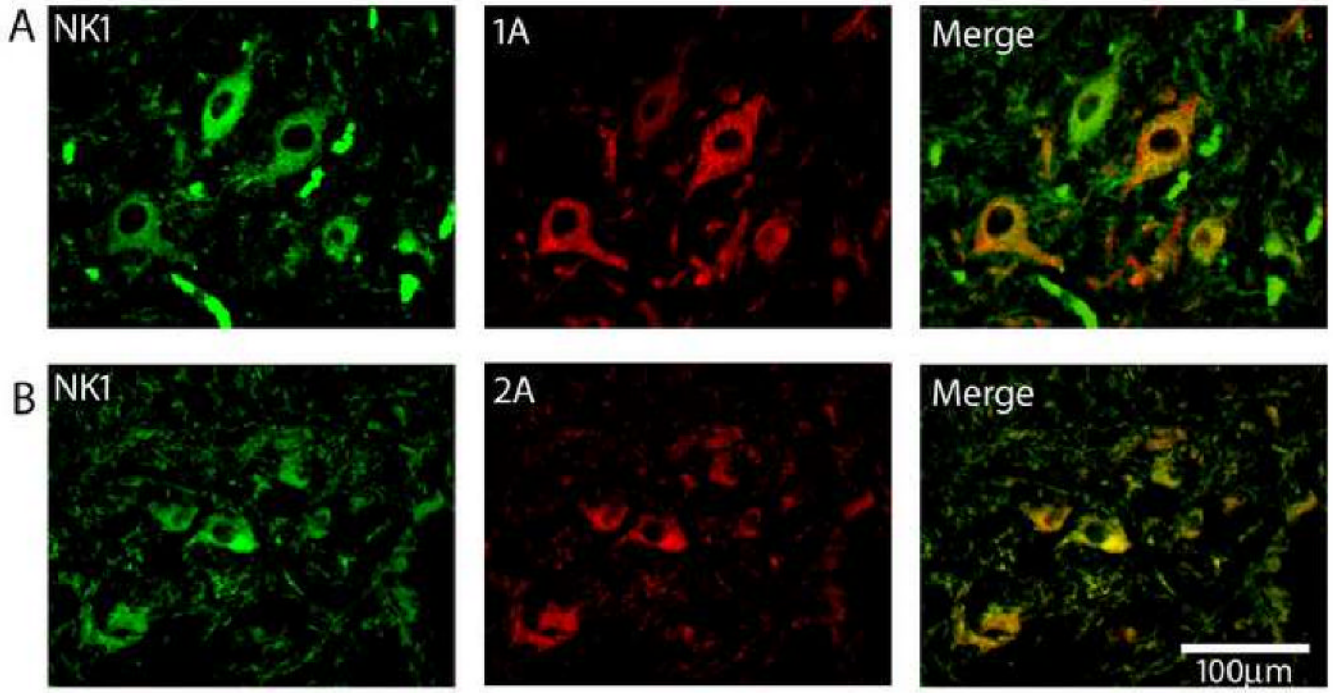

Figure 3.

Double-label immunofluorescent staining of putative preBötC neurons in the human infant PGCL with immunoreactivity for multiple neurotransmitter receptors that modulate preBötC function in rats. NK1 receptor immunofluorescent neurons (red) in the PGCL co localize with **A.** 5-HT_{1A} receptors, **B.** 5-HT_{2A} receptors. Images at ×40.

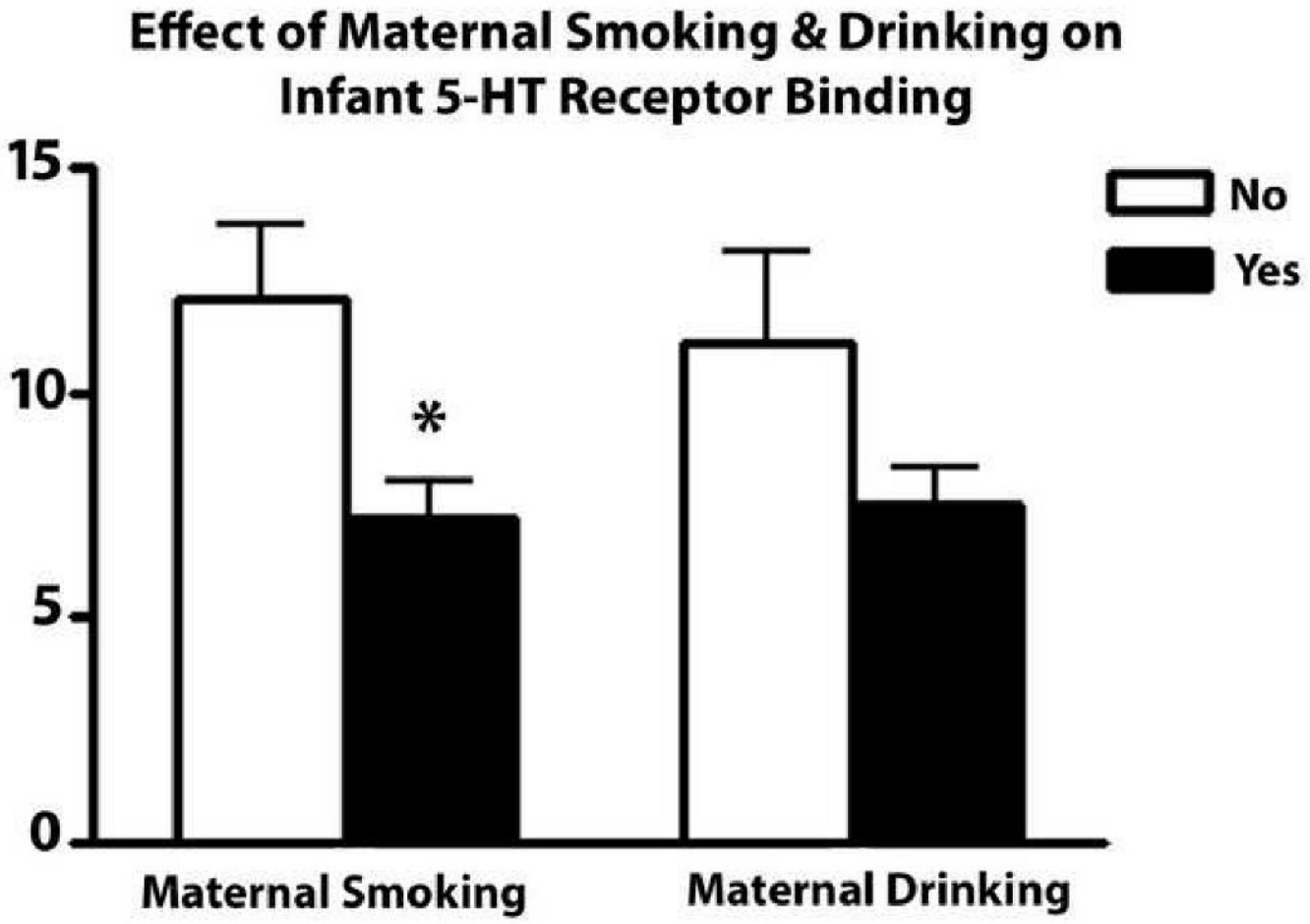

Figure 4. 5-HT receptor binding is significantly lower in the arcuate nucleus of infants exposed to cigarette smoke prenatally

Graphs comparing the effects of prenatal smoking and prenatal alcohol on the effects of 5-HT receptor binding measured with ^{3}H LSD autoradiography in the infant postnatally. Maternal smoking during pregnancy is associated with a 40% reduction (*p=0.011) and maternal alcohol ingestions during pregnancy is associated with a 32% reduction (p=0.075) in 5-HT receptor binding postnatally in infants.

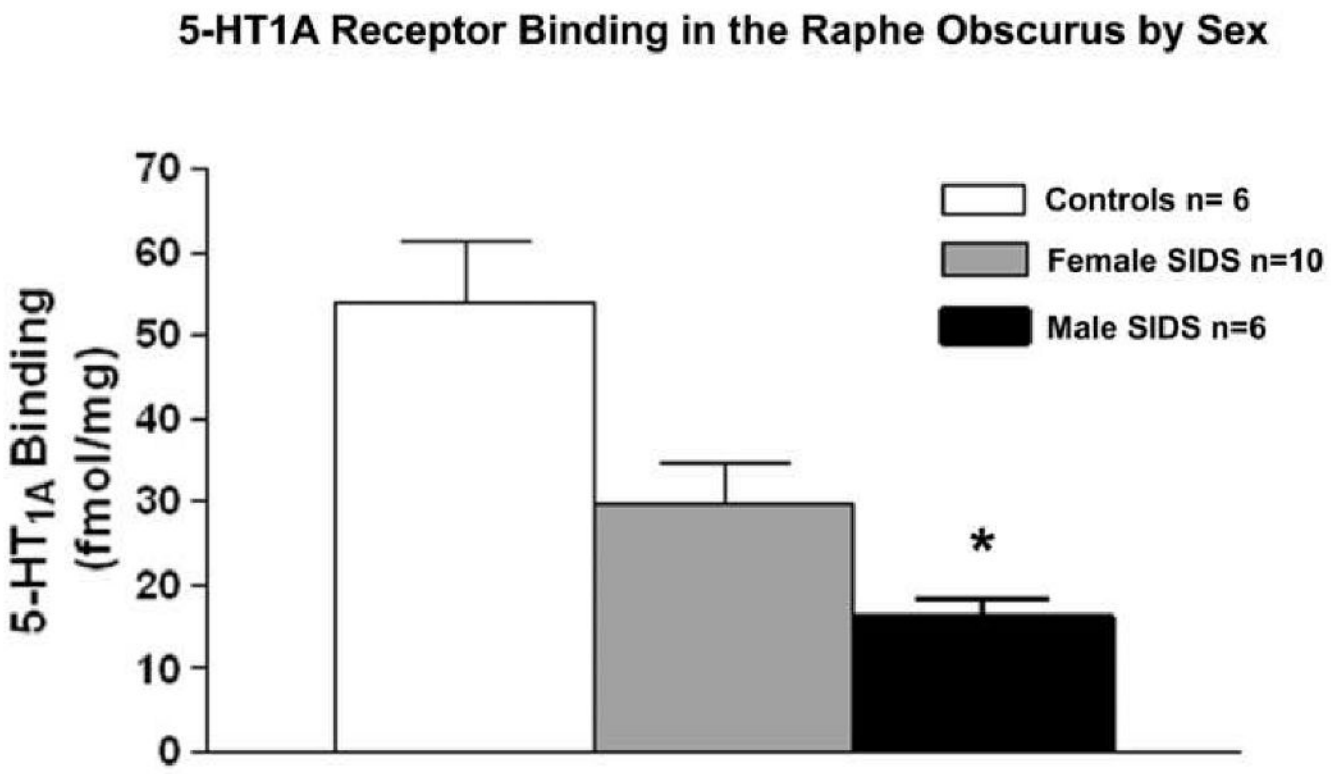

Figure 5. 5-HT$_{1A}$ receptor binding is lower in male SIDS cases

Graph comparing 5-HT$_{1A}$ receptor binding density measured with ^{3}H 8-OH DPAT autoradiography in the raphé obscurus in male and female SIDS cases compared to controls infants. 5-HT$_{1A}$ receptor binding density in male SIDS infants is significantly lower compared to female SIDS infants (*p=0.04). 5-HT$_{1A}$ receptor binding in both male (p=0.02) and female (p=0.05) SIDS infants is significantly lower compared to controls.