Published in final edited form as:

J Chem Neuroanat. 2011 July ; 41(4): 182–199. doi:10.1016/j.jchemneu.2011.05.004.

The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis

Hannah C. Kinney, MD, Kevin G. Broadbelt, PhD, Robin L. Haynes, PhD, Ingvar J. Rognum, MD, and David S. Paterson, PhD

Department of Pathology Children's Hospital Boston and Harvard Medical School Boston, MA 02115

Abstract

The caudal serotonergic (5-HT) system is a critical component of a medullary “homeostatic network” that regulates protective responses to metabolic stressors such as hypoxia, hypercapnia, and hyperthermia. We define anatomically the caudal 5-HT system in the human medulla as 5-HT neuronal cell bodies located in the raphé (raphé obscurus, raphé magnus, and raphé pallidus), extra-raphé (gigantocellularis, paragigantocellularis lateralis, intermediate reticular zone, lateral reticular nucleus, and nucleus subtrigeminalis), and ventral surface (arcuate nucleus). These 5-HT neurons are adjacent to all of the respiratory- and autonomic-related nuclei in the medulla where they are positioned to modulate directly the responses of these effector nuclei. In the following review, we highlight the topography and development of the caudal 5-HT system in the human fetus and infant, and its inter-relationships with nicotinic, GABAergic, and cytokine receptors. We also summarize pediatric disorders in early life which we term “developmental serotonopathies” of the caudal (as well as rostral) 5-HT domain and which are associated with homeostatic imbalances. The delineation of the development and organization of the human caudal 5-HT system provides the critical foundation for the neuropathologic elucidation of its disorders directly in the human brain.

Keywords

Arcuate nucleus; cytokines; fetal alcohol syndrome; γ -aminobutyric acid; nicotinic receptors; serotonopathy; sudden infant death syndrome

Introduction

Homeostasis refers to the ability of an organism to maintain a constant internal environment, thereby allowing survival over a wide range of external environmental conditions. It becomes self-sufficient at the moment of birth when the fetus takes the first breath in the extrauterine world and begins to adjust instantaneously and independently to the myriad of changing metabolic demands. Based upon the Greek word meaning “similar” (homeo) and “standing still” (stasis), homeostasis was formalized as a concept in the late nineteenth and early twentieth century by Walter Bradford Cannon and Claude Bernard, the latter who

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Corresponding Author: Hannah C. Kinney, MD Department of Pathology Enders Building 1112 300 Longwood Avenue Boston, MA 02115 Telephone: 617 919-4508 FAX: 617 730-0168 Hannah.kinney@childrens.harvard.edu.

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likewise introduced the concept of the internal milieu (Cannon, 1929; Gross, 1998). Since their time, our understanding of chemical mediators, anatomic regions, and mechanisms that participate in homeostasis, including in humans, has exponentially increased, as well our insight into the time-tables and programs of homeostatic development. Receptor systems that sense deviations in the internal milieu (e.g., in oxygen [O₂], carbon dioxide [CO₂], glucose, and temperature levels) have been defined, as well as the effector systems that are the final common pathway in mediating adjustments. Major focus has been placed upon the brain as the “control center” which sets the range at which a particular parameter, e.g., CO₂, is maintained, and determines the protective response to deviations from this range, e.g., hypercarbia. In addition, attention has been given to the developmental changes in the physiology and chemical anatomy of relevant brain regions in the first months following birth, the critical period in homeostasis when the fetus makes the transition to extraplacental life.

The serotonergic (5-HT) system primarily concentrated in the medulla oblongata—the so-called “caudal 5-HT system”, “medullary 5-HT system”, or B1–3 of the classic 5-HT brainstem neurons—is now recognized as a key component of the brain's control systems of homeostasis (Azmitia, 1999; Kinney *et al.*, 2009; Lovick, 1997; Mason, 2001) (Fig. 1). Extensive experimental data implicate the caudal 5-HT system in homeostasis and respiratory and autonomic regulation, including upper airway control, respiration (including via modulation of the preBötzinger complex, the putative central rhythm generator of respiration), autoresuscitation; central chemoreceptor responses to hypercapnia and hypoxia, cardiovascular control, pain, motor function, and thermoregulation (Bradley *et al.*, 2002; Corcoran *et al.*, 2009; Cummings *et al.*, 2010; Depuy *et al.*, 2011; Dergacheva *et al.*, 2009; Erickson *et al.*, 2007; Erickson and Sposato, 2009; Hilaire *et al.*, 2010; Hodges *et al.*, 2011; Hodges and Richerson, 2010; Hodges *et al.*, 2008; Hodges *et al.*, 2009; Pena and Ramirez, 2002; Penatti *et al.*, 2006; Ptak *et al.*, 2009; Richerson *et al.*, 2001; Taylor *et al.*, 2005; Tryba *et al.*, 2006). Serotonin is also involved in synaptic adjustments to hypoxia: long-term facilitation, for example, is an enhancement of ventilation or respiratory motor output (measured in respiratory nerve or hypoglossal discharge) that persists for hours after intermittent hypoxia, and is mediated by 5-HT via its release from the caudal raphé (Baker-Herman and Mitchell, 2002; Fuller *et al.*, 2001). The caudal 5-HT system is interconnected with other brain regions and neurotransmitter systems that influence homeostasis, including hypothalamic and limbic sites (Berthoud *et al.*, 2005; Horiuchi *et al.*, 2006; Morrison and Nakamura, 2011) (Fig. 1). Specific hypothalamic nuclei, for example, project to the raphé obscurus, raphé magnus, and/or raphé pallidus to affect cardiovascular, thermal, and other homeostatic responses (Horiuchi *et al.*, 2006; Morrison and Nakamura, 2011).

The homeostatic role of the caudal 5-HT domain is in contradistinction to the roles played in cognition, waking, mood, and cerebral blood flow by the rostral 5-HT domain in the upper pons and midbrain which projects diffusely and rostrally to the cerebral cortex, thalamus, hypothalamus, basal ganglia, hippocampus, and amygdala (Hornung, 2003; Tork and Hornung, 1990). The distinction between the caudal and rostral 5-HT domains is supported by evidence for different molecular profiles, developmental origins, and migration pathways (Hornung, 2003; Jensen *et al.*, 2008; Tork and Hornung, 1990; Wylie *et al.*, 2010). Still, neuroanatomic interconnections exist between the caudal and rostral 5-HT domains (Vertes *et al.*, 1999), as well as between the caudal 5-HT domain and (rostral) hypothalamic and limbic sites (Hermann *et al.*, 1997). Moreover, some functional overlap exists between the two 5-HT domains. While historically the rostral 5-HT domain has been considered instrumental in mediating arousal as part of the ascending activating systems, for example, mounting evidence also implicates the caudal 5-HT domain in the modulation of sleep and waking (Brown *et al.*, 2008; Darnall *et al.*, 2005). In turn, evidence suggests that the rostral 5-HT domain plays a role in chemosensitivity to CO₂ previously attributed to medullary 5-

HT neurons (Buchanan and Richerson., 2010; Severson *et al.*, 2003). Nevertheless, given the experimental evidence for the major role of the caudal 5-HT system in homeostasis, including during development, we propose that deficits in this system lead to imbalances in respiratory, cardiovascular, and/or metabolic regulation, including in response to stress, in the pediatric age-range, particularly in the first days and months following birth. In the following review, we highlight the topography and development of the caudal 5-HT system in the human fetus and infant, and summarize pediatric 5-HT disorders which involve homeostatic imbalances.

The Topography of 5-HT Neurons in the Infant Medulla

Located within the crowded confines of the medulla is arguably the highest concentration of nuclei in the brain that mediate respiratory and autonomic function. These nuclei include the nucleus of the solitary tract (visceral sensory input and cardiorespiratory integration), dorsal motor nucleus of the vagus (preganglionic parasympathetic outflow), preBötzinger complex (respiratory rhythm generation), hypoglossal nucleus (upper airway patency, including during sleep), nucleus ambiguus and periaambiguous region (ventral respiratory group, vagal cardiomotor neurons, and control of upper airway musculature in the larynx and pharynx), and neuronal populations in the reticular subnuclei in the rostral and caudal ventrolateral medulla critical for blood pressure regulation (Figs. 1 and 2). The caudal 5-HT system interfaces directly with these effector nuclei. It also interfaces with the autonomic nervous system via projections to the dorsal motor nucleus of the vagus (preganglionic parasympathetic outflow) and intermediolateral column in the spinal cord (preganglionic sympathetic outflow) (Fig. 1); in addition, caudal 5-HT neurons project to the nucleus of the solitary tract, the visceral sensory input of the autonomic nervous system (Fig. 1). Overall, the caudal 5-HT neurons are positioned to integrate and modulate multiple respiratory, heart rate, blood pressure, and temperature parameters simultaneously via projecting to the nearby effector nuclei (Fig. 2). The neuroanatomic finding that single 5-HT neurons in the raphé obscurus in rat medullary slices innervate both the hypoglossal nucleus and preBötzinger complex via axonal bifurcation support this concept (Ptak *et al.*, 2009).

We define anatomically the caudal 5-HT system in the human infant as 5-HT neuronal cell bodies in the medulla that are located in the raphé (raphé obscurus, raphé magnus, and raphé pallidus), extra-raphé (gigantocellularis, paragigantocellularis lateralis, and intermediate reticular zone, lateral reticular nucleus, and nucleus subtrigeminalis), and ventral surface (arcuate nucleus) (Kinney *et al.*, 2007) (Fig. 2). Our laboratory has characterized the ventral 5-HT neuronal populations within the arcuate nucleus in the human infant medulla as the putative homologue of respiratory chemosensitive zones in experimental animals (Filiano *et al.*, 1990; Paterson *et al.*, 2006a; Zec *et al.*, 1997). The human arcuate nucleus along the ventral surface has been considered historically as a precerebellar relay nucleus derived from downwardly displaced pontine neurons, and as rhombic lip derivatives via ventromedial migrations (Filiano *et al.*, 1990). Yet, it contains neurons that are cytologically and positionally similar to those in the respiratory chemosensitivity zones of the ventral medullary surface in the cat (Filiano *et al.*, 1990) (Fig. 3). Moreover, single or clustered 5-HT neurons are embedded within the arcuate nucleus and comprise about 5% of the neurons at this site (Fig. 4) (Kinney *et al.*, 2007). This observation is noteworthy because 5-HT neurons at the medullary ventral surface and in the midline (raphé) in experimental animals are now known to be preferentially chemosensitive to CO₂, and while not the only central chemosensitive neurons, they play critical modulatory roles (Bradley *et al.*, 2002; Richerson *et al.*, 2001; Taylor *et al.*, 2005). In this regard, 5-HT neurons in the arcuate nucleus demonstrate processes that appear to penetrate the glial limitans and extend into the subarachnoid space where they are in the position to “sense” CO₂ levels in the cerebrospinal fluid (CSF) (Kinney *et al.*, 2007). In the human infant medulla, scattered, single, fusiform 5-

HT neurons extend ventrally from the raphé to line the median and ventral surface of the pyramids in the arcuate nucleus (Fig. 4) (Kinney *et al.*, 2007), forming a continuum of raphé neurons ventrally. Past comparative studies suggest that the human arcuate nucleus is indeed homologous to the ventral raphé pallidus or raphé ventralis in several species, notably the pygmy primate (Kinney *et al.*, 2007). Utilizing the DiI track tracing method in the fetal human brainstem, we also found that the connectivity of the arcuate nucleus is inter-related to the raphé obscurus and pallidus (Zec *et al.*, 1997), supporting the idea that arcuate nucleus is a ventral extension of the caudal raphé.

In addition to 5-HT neurons at the ventral surface, 5-HT neurons in the raphé and extra-raphé have been implicated in chemosensitivity (Hodges and Richerson, 2010; Penatti *et al.*, 2006; Taylor *et al.*, 2005). In this regard, the 5-HT neurons form three distinct columns in the rostrocaudal plane in the ventral view of the human infant medulla (Fig. 5). The lateral columns are formed by 5-HT neurons of the paragigantocellularis lateralis at the very ventrolateral surface at the rostral medulla, and are continuous with 5-HT neurons within the lateral reticular nucleus and nucleus subtrigeminalis (Fig. 5); the 5-HT neurons in the midline column are in the raphé (Fig. 5). The topographic pattern of the ventrolateral 5-HT neurons overlaps with the historical M, S, and L chemosensitive zones of the cat and large arterial vascular distribution in the rat (Bradley *et al.*, 2002) (Fig. 5). Moreover, immunocytochemical observations suggest spatial homology of 5-HT neurons between the rat and human ventral medulla in the midline and ventrolateral positions (Fig. 5). Comparative neuroanatomic studies further suggest that the paragigantocellularis lateralis and gigantocellularis (which are situated along the ventral surface of the rodent and feline medulla) have been displaced dorsally from the ventral surface in the human due to the evolutionary “expansion” of the inferior olive as cortico-olivary projections intensified (Niblock *et al.*, 2005).

The Development of the 5-HT System in the Human Fetal and Infant Medulla

Medullary 5-HT neurons appear as early as 5–7 gestational weeks in the embryo (Fig. 6) (Kinney *et al.*, 2007). At 7 gestational weeks, 5-HT neurons form two “plates” along either side of the midline as the primordia of the raphé obscurus (Fig. 6). At this time-point, 5-HT neurons are also widely scattered in the ventrolateral and ventromedial tegmentum, representing the primordia of the paragigantocellularis lateralis and gigantocellularis (Fig. 6). By 20 gestational weeks, the adult-like raphé and extra-raphé configuration is qualitatively “in place”. With maturation, including into the postnatal period, there is a shift in the ratio of morphological subtypes, with a significant decrease in granular (immature) 5-HT neurons and a marginal increase in fusiform 5-HT neurons, suggesting differentiation into more complex forms with age (Kinney *et al.*, 2007). The 5-HT neurons in the caudal raphé are known to arise in and migrate ventrally from the basal plate (Jensen *et al.*, 2008). In support of this origin in the human, we found single 5-HT neurons in very close proximity to the site of the basal plate in the fetal period (Kinney *et al.*, 2007). The possible origin of 5-HT neurons in the rhombic lip with surface migration ventrally to the raphé and extra-raphé has not been confirmed in 5-HT cell lineage studies with modern gene mapping strategies (Jensen *et al.*, 2008). Simultaneous with the topographic changes in 5-HT neurons are marked neurochemical changes in other 5-HT markers both pre- and postnatally (Paterson *et al.*, 2004; Zec *et al.*, 1996). There is a significant reduction in the density of ³H-lysergic acid diethylamide (LSD) binding to 5-HT_{1A-1D} and 5-HT₂ receptors from midgestation to the neonatal period, and from infancy to childhood (Fig. 7). The binding density, however, is essentially constant across infancy (Fig. 7). There are no age-related changes in 5-HT_{1A} receptor binding (Duncan *et al.*; Paterson *et al.*, 2006b), or in 5-HT transporter binding in infancy (Paterson *et al.*, 2004); data for these two markers are not available in the fetal period.

5-HT_{1A} and 5-HT_{2A} Receptor Binding in the Infant Medulla

The specific effects of 5-HT upon autonomic and respiratory effector nuclei in the medulla are mediated via 5-HT receptors, of which at least 7 families have been identified to date (Pytliak *et al.*, 2011). With the exception of the 5-HT₃ receptor, which forms an ion-channel receptor complex, all 5-HT receptors are G-protein coupled and initiate cellular responses to 5-HT by induction of second messenger cascades (Barnes and Sharp, 1999). Extensive evidence in animals indicates that the 5-HT_{1A} and 5-HT_{2A} receptor subtypes each play major roles in medullary 5-HT mediated homeostatic function (Cayetanot *et al.*, 2002; Darnall *et al.*, 2005; Pena and Ramirez, 2002; Tryba *et al.*, 2006). The 5-HT_{1A} receptor is generally considered to be inhibitory; it is negatively coupled to adenylate cyclase and when activated, inhibits the formation of cyclic AMP, thereby reducing neuronal excitability (Barnes and Sharp, 1999). Although it is distributed to both 5-HT and non-5-HT neurons in the brainstem, it is predominantly localized to the soma and dendrites of 5-HT neurons where it functions as an inhibitory autoreceptor, regulating neuronal firing and synaptic release of 5-HT (Blier *et al.*, 1998; Darnall *et al.*, 2005; Paterson *et al.*, 2006a). In contrast, the 5-HT_{2A} receptor is considered to be excitatory; upon activation it stimulates the activity of protein kinase C and mobilizes intracellular calcium stores, thereby increasing neuronal excitability (Barnes and Sharp, 1999). The 5-HT_{2A} receptor functions predominantly as an excitatory postsynaptic receptor localized to non-5-HT neurons in the medulla, where it mediates many of the effects of 5-HT (Cornea-Hebert *et al.*, 1999; Pena and Ramirez, 2002; Tryba *et al.*, 2006).

Using tissue receptor autoradiography with the 5-HT_{1A} agonist, ³H-8-hydroxy-2-[di-N-propylamine] tetralin (³H-8-OH-DPAT), we identified that 5-HT_{1A} receptors are predominantly localized to nuclei containing 5-HT neuron cell bodies in the infant medullary 5-HT system (Fig 8), consistent with their role as somato-dendritic autoreceptors (Paterson *et al.*, 2004). The highest density of 5-HT_{1A} receptor binding is observed in the raphe obscurus, the site of the highest density of 5-HT neurons in the medulla, with intermediate binding density in the lateral medullary 5-HT nuclei (i.e., gigantocellularis, paragigantocellularis lateralis, and intermediate reticular zone), and low binding density in nuclei that do not contain 5-HT neurons but receive significant innervation from medullary 5-HT neurons (i.e., hypoglossal nucleus, dorsal motor nucleus of the vagus, and nucleus of the solitary tract) (Fig 8). Immunocytochemistry confirms that 5-HT_{1A} receptors are expressed on 5-HT neuronal cell bodies in these regions (Fig. 9). In contrast, autoradiography with ¹²⁵I-1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (¹²⁵I-DOI) reveals that 5-HT_{2A} receptor binding density is highest in the hypoglossal nucleus, dorsal motor nucleus of the vagus, and nucleus of the solitary tract, with moderate to low density in the extra-raphé 5-HT nuclei (i.e., gigantocellularis, paragigantocellularis lateralis, and intermediate reticular zone), and arcuate nucleus, and with negligible density in the raphe obscurus (Fig. 8) (Paterson and Darnall, 2009). Double-label immunofluorescence reveals that 5-HT_{2A} receptors are predominantly expressed by non-5-HT neurons, although a subpopulation of 5-HT neurons in the raphe and extra-raphé co-localize 5-HT_{2A} receptors (Fig. 9).

5-HT Transporter Binding in the Infant Medulla

The 5-HT transporter is arguably the key element in the regulation of 5-HT neurotransmission as it determines the level of synaptic 5-HT via transport of released 5-HT back into the neuron (Blakely *et al.*, 1994). The 5-HT transporter is expressed predominantly in peri-synaptic sites on 5-HT neuronal terminals and thus is an important marker of 5-HT neuronal innervation (Zhou *et al.*, 1998). In our laboratory, we have characterized the distribution of the 5-HT transporter in the human infant medulla using

tissue section autoradiography with ^{125}I - [3 β -(4-iodophenyl) tropane-2 β -carboxylic acid methyl ester] (^{125}I RTI-55) (Paterson *et al.*, 2004). We observed 5-HT transporter binding sites throughout the medullary 5-HT system, including in both 5-HT neuron source nuclei and 5-HT projection nuclei (Fig. 8). Consistent with 5-HT $_{1A}$ receptor distribution, the highest density of 5-HT transporter binding is present in the raphé obscurus. The density of binding in the hypoglossal nucleus and dorsal motor nucleus of the vagus relative to binding in the raphé, however, is substantially higher for the 5-HT transporter than for 5-HT $_{1A}$ receptors, and is more consistent with the distribution on 5-HT $_{2A}$, as opposed to 5-HT $_{1A}$, receptor binding sites. These observations suggest that effector nuclei, e.g., hypoglossal nucleus, receive significant innervation from medullary 5-HT neurons, and that 5-HT $_{2A}$ receptors in the human infant medulla are predominantly postsynaptic to 5-HT axon terminals.

Anatomic Relationships between the Serotonergic and Nicotinic Systems

Neuronal nicotinic receptors (nAChRs) are pentameric; ligand-gated ion channels comprised of 5 subunits encoded by 9 α ($\alpha 2$ - $\alpha 9$) and 3 β ($\beta 2$ - $\beta 4$) genes. (Gotti *et al.*, 2006). They can be heteromeric, consisting of a mixture of 2 α and 3 β subunits), or homomeric, consisting 5 $\alpha 7$ subunits (Gotti *et al.*, 2006). Each nAChR subtype displays unique physiological and pharmacological properties determined by their subunit composition, as well as distinct neuroanatomic distributions (Cimino *et al.*, 1995; Hellstrom-Lindahl and Court, 2000). There is considerable functional evidence for important nicotinic-5-HT interactions in animal models (Cordero-Erausquin and Changeux, 2001; Duncan *et al.*, 2009). Nicotine exposure, for example, increases 5-HT release and alters 5-HT neuronal firing in a dose-dependent manner in animal models (Cimino *et al.*, 1995).

We have mapped the distribution of nAChR subtypes in the infant medullary 5-HT system using autoradiography with ^3H -nicotine which binds to all nAChRs subtypes, ^3H -epibatidine ($\alpha 2$ -4, $\beta 2$, $\beta 4$), 3H cytosine ($\alpha 4\beta 2$), and ^{125}I α -bungarotoxin ($\alpha 7$) (Fig 9) (Duncan *et al.*, 2008; Kinney *et al.*, 1993). For all nAChRs, the highest density of binding is observed in the inferior olivary complex, with the exception of the $\alpha 7$ nAChR in which the highest density is present in the hypoglossal nucleus and nucleus of the solitary tract. Tritiated-nicotine binding is highest in the olivary complex and lowest in the raphé obscurus, with negligible binding in the arcuate nucleus (Fig. 8). In contrast, ^3H -epibatidine binding (displaying affinity for nAChRs with the $\alpha 2$ -4, $\beta 2$, $\beta 4$ subunits) is prominent in all medullary nuclei, with similarly high binding as ^3H -nicotine binding in the olivary complex (Fig. 8). Notably, ^3H -epibatidine binding is visually distinct in the arcuate nucleus. Tritiated-cytosine binding is uniformly low in all medullary nuclei analyzed with the exception of the olivary complex (Fig. 8). The binding pattern of the ^{125}I - α -bungarotoxin to $\alpha 7$ nAChRs is markedly different to that of the other nAChR radioligands: binding is highest in the hypoglossal nucleus and nucleus of the solitary tract and lowest in the arcuate nucleus (Fig. 8). Double-label immunofluorescence reveals that the $\alpha 4$ nAChR subunit is expressed on the soma and dendrites of both 5-HT and non-5-HT neurons in the raphé, extra-raphé, and arcuate nucleus (Fig. 9). Thus, nicotinic receptors are present in medullary nuclei that contain 5-HT cell bodies, as well effector nuclei that receive extensive 5-HT projections.

Anatomic Relationships between the Serotonergic and GABAergic Systems

Animal studies indicate multiple interactions between GABA and 5-HT neurons, including in respiration, thermoregulation, and autonomic function (Broadbelt *et al.*, 2010; Liu *et al.*, 2000; Serrats *et al.*, 2005). In the human caudal 5-HT system, GABAergic interneurons are intermingled among the 5-HT source neurons, as well as non-5-HT neurons in the 5-HT projection sites (Broadbelt *et al.*, 2010). Only 6% of the 5-HT neurons in the caudal raphé of

the human infant co-express GABA (Broadbelt *et al.*, 2010). Across late fetal and early infant development, GABA_{Aα1} and GABA_{Aα3} receptor subtypes are expressed throughout the medullary 5-HT system, and tissue receptor autoradiography demonstrates that GABA_A receptor binding is ubiquitous across the medullary nuclei in the human infant (Figs. 8 and 9) (Broadbelt *et al.*, 2010).

Inter-relationships between the Serotonergic System and Cytokines

Cytokines orchestrate immune responses to microbial invasion and other insults and coordinate these responses with those of other physiological systems, including the autonomic nervous system, in the protection of the organism against tissue injury (Buller *et al.*, 2003; Dunn *et al.*, 2005). They also mediate “sickness behaviour”, including fever, anorexia, excessive sleepiness, blunted arousal, depressed respiration, and lowered heart rate, which is thought to protect the organism during systemic illness by dampening excessive metabolic demands and thereby speeding repair and recovery (Dunn *et al.*, 2006; Dunn *et al.*, 2005; Vollmer-Conna *et al.*, 2004)—a form of homeostasis. Cytokines determine this sickness behaviour by binding to endogenous cytokine receptors on neuronal populations in the hypothalamus and/or brainstem that mediate respiration, autonomic function, satiety, sleep, and arousal (Rognum *et al.*, 2009). The cytokines which act within the brain in response to tissue injury are produced by astrocytes, endothelial cells, microglia, and/or peripheral immune cells which enter the brain in response to neural signals of tissue damage. Exaggerated or prolonged immune responses are not uncommonly associated with a hypermetabolic state with increased O₂ consumption, increased CO₂ production, and increased energy expenditure (Bauer *et al.*, 2002; Moriyama *et al.*, 1999).

Our laboratory has investigated the cellular expression of interleukin-6 receptors (IL-6Rs) and their signal transducer gp 130 (both necessary for IL-6 signalling) in the caudal 5-HT system of the human infant medulla as a representative marker of the interface between cytokines and homeostatic control (Rognum *et al.*, 2009). During infection, peripherally produced IL-6 may cross the blood brain barrier and bind to IL-6Rs on 5-HT neurons that mediate homeostasis in response to the infectious “stressor” and potentially mediate sickness behaviour. In support of this possibility, the intraperitoneal injection of IL-6 in rats increases 5-HT metabolism in the brainstem (Wang and Dunn, 1998). We found ubiquitous expression of IL-6Rs and gp 130 by neurons in all regions in the infant medulla, including those effector nuclei critical to respiratory and autonomic control, and those that contain 5-HT source neurons (Rognum *et al.*, 2009). Serotonergic neurons in the caudal 5-HT system, including in the raphe obscurus and arcuate nucleus, express IL-6Rs on somata and processes, indicating the site of IL-6/5-HT interaction (Fig. 9).

Pediatric Disorders of the Medullary 5-HT System

While much attention has focused upon the rostral 5-HT system relative to disorders of cognition and mood in children and adults, less focus has been placed upon homeostatic impairments in developmental disorders of the caudal 5-HT system (Table 1) (Fig. 10). Indeed, pediatric 5-HT disorders may result from combined defects in the caudal and rostral 5-HT domains (Table 1). Alternatively, these disorders may potentially result from defects restricted mainly to either the rostral or caudal 5-HT system—a predicted finding based upon the differences between the two 5-HT domains in developmental time-tables, origins, migration pathways, connectivity, and molecular regulation (see above) (Table 1). While there is some overlap in the functions of the caudal and rostral 5-HT domains (see above), we believe it is clinically valuable when evaluating children with potential 5-HT disorders to consider the particular disorder relative to the anatomic site of the lesion—caudal and/or rostral—and the resulting complex of specific signs and symptoms.

Brainstem 5-HT disorders in early life can be conceptualized as reflecting the “intersection” of disease and development, that is, the end-result of the adverse effects of environmental and/or genetic insults upon the trajectory of developmental programs mediated by 5-HT. Indeed, 5-HT is well-recognized to play a critical role as a growth factor in early cell division, migration, and differentiation in the brain (Lauder, 1990; Sodhi and Sanders-Bush, 2004). Experimental precedent for adverse genetic effects upon 5-HT development, for example, is demonstrated by mouse mutants in which excessive 5-HT brain levels due to genetic disruptions result in altered maturation of the medullary respiratory network (Bou-Flores *et al.*, 2000). Below, we highlight pediatric disorders in early life that affect the caudal 5-HT system as based upon clinical presentation, 5-HT-related biomarkers, and/or tissue evidence from autopsy, *in vivo* neuroimaging studies, and/or animal models. While 5-HT dysfunction has been implicated in many psychiatric disorders which can originate in early life, e.g., panic disorder, depression, and attention deficit hyperactivity disorder (Nikolaus *et al.*, 2009), and involve the rostral 5-HT domain and its limbic, cortical, and basal ganglia projections, their discussion is beyond the scope of this review. Of note, while many of these psychiatric disorders demonstrate autonomic and/or respiratory dysfunction, little information is known about potential caudal 5-HT deficits.

Neurological disorders of inborn errors of 5-HT metabolism

Serotonin in brainstem 5-HT neurons is synthesized from the amino acid tryptophan (acquired through the diet via passage across the blood brain barrier) (Fig. 10). The first step to 5-hydroxytryptophan (5-HTP) involves the rate-limiting enzyme, tryptophan hydroxylase (TPH2), and the second step from 5-HTP to 5-HT involves the pyridoxine-dependent enzyme aromatic L-amino acid decarboxylase (AADC) (Fig. 10) (Hyland, 2007; Lamers and Wevers, 1998). Both TPH2 and tyrosine hydroxylase, the key biosynthetic enzyme for catecholamine neurotransmitters, require tetrahydrobiopterin (BH4) for their activity (Fig. 10). Five-hydroxytryptophan in 5-HT synthesis and L-dopa in catecholamine synthesis are decarboxylated by AADC to 5-HT and dopamine, respectively (Hyland, 2007). The catabolism of 5-HT is performed via the formation of metabolites by aldehyde dehydrogenase (ALD) or monoamine oxidase (MAO) (Fig. 10). The major metabolite of 5-HT is 5-hydroxy-indoleacetic acid (5-HIAA) whose concentration in CSF is thought to reflect brain 5-HT turnover (Lamers and Wevers, 1998). Consequently, 5-HIAA measurement in the CSF provides a tool for detecting and monitoring diseases that affect 5-HT metabolism (De Grandis *et al.*, 2011; Lamers and Wevers, 1998).

Several inborn errors of BH4 metabolism have been reported in children (Lamers and Wevers, 1998; Shintaku, 2002)(Fig. 10). Given the role BH4 cofactors in 5-HT and catecholamine synthesis, these disorders reflect 5-HT, dopamine, and norepinephrine deficiencies. Typically they present in the neonatal period with central dysfunction, including seizures, hypotonia, dystonia, chorea, athetosis, hypokinesia, and oculogyric crisis; they also present with autonomic and state dysfunction, including hypersalivation, hyperthermia, and somnolence. Progressive neurological deterioration is followed by early death in infancy; sudden death has also been reported (Pearl *et al.*, 2007). There are a few reports of successful treatment of BH4 defects with 5-hydroxytryptophan and L-Dopa in conjunction with a peripheral decarboxylase inhibitor (Lamers and Wevers, 1998).

An inborn deficiency of AADC is inherited in an autosomal recessive pattern, with up to 24 reported mutations (Brun *et al.*, 2010; Pons *et al.*, 2004) (Fig. 10). Given the role of AADC in both 5-HT and catecholamine metabolism, this disorder also reflects dopamine and norepinephrine deficiencies (Brun *et al.*, 2010). Typically AADC deficiency presents in infancy with developmental delay, motor impairments (ptosis, hypotonia, and extrapyramidal disorders), sleep disturbances, and autonomic instability (hypotension, hypersalivation, diaphoresis, hypothermia, and cardiorespiratory arrest) (Pons *et al.*, 2004;

Swoboda and Hyland, 2002). Approximately one-fourth of patients demonstrate neuroimaging abnormalities, including cerebral atrophy and hypomyelination (Brun et al., 2010). Treatment programs involving monoamine replacement and MAO inhibition are generally not successful (Pons *et al.*, 2004; Swoboda and Hyland, 2002). The movement abnormalities are attributed to dopaminergic deficiency and basal ganglia dysfunction (Brun et al., 2010); yet, caudal 5-HT defects could contribute to the autonomic dysfunction. Elucidation of the rostral and caudal 5-HT domains in BH4 and AADC deficiencies in human neuropathologic studies are not available.

Autism spectrum disorders

Autism is a neurodevelopmental disorder with onset in early life that is characterized by deficits in social interactions and communication (Bal et al., 2010; Levy *et al.*, 2009). It is associated with developmental delay, abnormal emotional facial processing, and repetitive and stereotyped patterns of behavior (Bal *et al.*, 2010; Levy *et al.*, 2009). Abnormalities in cardiorespiratory function and state regulation also occur, including alterations in sinus respiratory arrhythmia, parasympathetic and sympathetic cardiac balance, and heart rate responses in emotional processing (Bal et al., 2010; Bolte *et al.*, 2008; Ming *et al.*, 2005; Palkovitz and Wiesenfeld, 1980). Sleep abnormalities include prolonged sleep onset, sleep fragmentation, excessive daytime sleepiness, and sleep-disordered breathing (Liu *et al.*, 2006; Ming *et al.*, 2005). While autism likely involves complex neurotransmitter interactions (McDougle *et al.*, 2005), substantial evidence implicates a major role for 5-HT dysregulation (Cook and Leventhal, 1996). Elevated whole blood 5-HT levels are found in 25–50% of autistic cases and their first-degree relatives (Burgess *et al.*, 2006; Cook and Leventhal, 1996), and positron emission topography reveals decreased cortical 5-HT levels in autistic children (Chugani *et al.*, 1999). Moreover, short-term dietary deficiency of tryptophan exacerbates repetitive behavior and augments anxious and unhappy feelings in autistic individuals (McDougle *et al.*, 1996). Treatment with selective serotonin uptake inhibitors (SSRIs), on the other hand, ameliorates repetitive and/or obsessive behaviors in some cases (Kolevzon *et al.*, 2006). Polymorphisms within the 5-HTTLPR promoter sequence, mutations in the coding sequence, or intronic mutations of the 5-HT transporter have been reported in autism (Murphy *et al.*, 2008; Prasad *et al.*, 2009). The case report of an autistic child with the heterozygous SLC64A gene Gly56Ala alteration plus the homozygous 5-HTTLPR L/L promoter variant is of special importance as daily oral treatment with 5-hydroxytryptophan (and carbidopa) led to marked clinical improvement in autistic behaviors and normalization of low 5-HIAA levels in the CSF (Adamsen *et al.*, 2011). While the cognitive and emotional components of autism implicate an abnormal rostral 5-HT domain, the autonomic and respiratory components suggest an impaired caudal 5-HT domain as well. Neuropathologic studies of autistic brains demonstrate overall increased weight, abnormalities of minicolumn formation in the cerebral cortex, underpopulation of Purkinje cells in the cerebellar cortex, and forebrain migration disturbances (Amaral *et al.*, 2008; Wegiel *et al.*, 2010). Yet, no studies to date report a systematic analysis of 5-HT markers in the forebrain and/or brainstem of autistic children at autopsy.

Rett syndrome

Rett Syndrome is a neurodevelopmental disorder characterized by gradual cognitive decline following normal development through the first 6 to 18 postnatal months; it is one of the most common causes of intellectual disabilities in females (Katz *et al.*, 2009; Trevathan and Naidu, 1988). Rett syndrome patients also demonstrate a spectrum of autonomic and respiratory dysfunction, including hyperventilation, abnormal heart rate variability, and sudden death (Guideri *et al.*, 2004; Katz *et al.*, 2009). The majority of Rett syndrome cases are caused by inactivating mutations in the methyl-CpG-binding protein 2 (MECP2) gene

(Amir *et al.*, 1999; Katz *et al.*, 2009). In limited postmortem neurochemical analysis in Rett Syndrome brains, reductions in 5-HT, as well as catecholamine, levels have been described in different regions, including the substantia nigra (Lekman *et al.*, 1989; Riederer *et al.*, 1985). Initial studies reporting reduced levels of 5-HT and 5-HIAA in the CSF in Rett Syndrome patients (Zoghbi *et al.*, 1985) have not been universally confirmed (Lekman *et al.*, 1989; Perry *et al.*, 1988; Temudo *et al.*, 2009). In our laboratory, we observed an abnormal developmental profile of 5-HT transporter binding in the dorsal motor nucleus of the vagus in Rett Syndrome patients compared to controls (Paterson *et al.*, 2005), supporting the idea that altered 5-HT innervation or 5-HT re-uptake at this site may contribute to the autonomic dysfunction in Rett Syndrome. We did not find, however, a decrease in 5-HT neurons in the raphe obscurus in affected patients compared to controls (Paterson *et al.*, 2005). Notably, administration of the 5-HT_{1A} receptor agonist Buspirone improved respiratory dysfunction in a patient with Rett Syndrome (Andaku *et al.*, 2005). Genetically engineered mice lacking the MECP2 gene display reduced levels of 5-HT, 5-HIAA, or other 5-HT markers and/or 5-HT-related autonomic and respiratory dysfunction (Abdala *et al.*, 2010; Bidon *et al.*, 2008; Katz *et al.*, 2009; Viemari *et al.*, 2005). Moreover, similar to Rett patients, administration of 5-HT_{1A} receptor agonists improves respiratory function and prolongs life in MECP null mice (Abdala *et al.*, 2010). The rostral and caudal 5-HT domains both appear to be affected in Rett Syndrome.

Prader-Willi Syndrome (PWS)

This syndrome is a maternally imprinted disorder resulting from a loss of paternal gene expression on chromosome 15q11–13. It is characterized by cognitive deficits, hypotonia, short stature, hypogonadism, infantile failure to thrive, and hyperphagia leading to morbid obesity in childhood (Goldstone *et al.*, 2004). Importantly, it is also associated with breathing deficits, rhythm instability, severe sleep apnea, and blunted respiratory responses to hypoxia and hypercarbia (Nixon and Brouillette, 2002); moreover, the breathing deficits are a risk factor for early sudden death (Nagai *et al.*, 2005; Schrandt-Stumpel *et al.*, 2004). Serotonin abnormalities are implicated in the pathogenesis of PWS by the report of elevated monoamine oxidase activity in platelets (Akefeldt and Mansson, 1998) and elevated 5-HIAA levels in the CSF in affected patients (Akefeldt *et al.*, 1998). The caudal 5-HT system is specifically implicated by abnormalities in the human paternal NECDIN gene, which is expressed in murine medullary 5-HT neurons and is deleted or inactivated in the PWS (Zanella *et al.*, 2008b). Necdin is an anti-apoptotic factor in early development and a growth factor that affects neuronal migration, axonal extension, and fasciculation (Zanella *et al.*, 2008a). Necdin-deficiency in mice induces central respiratory deficits analogous to clinical PWS (irregular rhythm, frequent apneas, and blunted respiratory regulation) and alters the 5-HT modulation of the respiratory rhythm generator; moreover, it alters 5-HT metabolism, as well as the morphology of 5-HT vesicles in medullary 5-HT neurons (Zanella *et al.*, 2008a; Zanella *et al.*, 2008b). Thus, the lack of Necdin expression induces perinatal 5-HT alterations that affect the maturation and function of the medullary respiratory network, inducing breathing impairments (Zanella *et al.*, 2008a; Zanella *et al.*, 2008b). In addition, 5-HT_{2C} receptor abnormalities are suggested in PWS due to the loss of 15q11–13 gene expression which is related to 5-HT_{2C} transcript editing (Morabito *et al.*, 2010). Site-specific editing of 5-HT_{2C} transcripts is increased in brain samples from both PWS patients and a mouse model of PWS, the latter which also displays deficits in 5-HT_{2C}-mediated behaviors (Morabito *et al.*, 2010). The role of the rostral 5-HT domain in cognitive deficits in patients with PWS is unknown.

Fetal alcohol syndrome (FAS)

Prenatal alcohol exposure leads to deficits in brain development, somatic growth, facial features, and organ formation under the rubric of fetal alcohol spectrum disorders (FASD)

(Guerri *et al.*, 2009). At the most severe end of the spectrum is FAS which is characterized by craniofacial dysmorphology, pre- and postnatal growth retardation, and severe neurobehavioral disabilities (Guerri *et al.*, 2009). The phenotypic variability of FASD, including intellectual impairments without facial dysmorphia, reflects differences in the timing, dose, and delivery pattern of alcohol exposure, as well as the simultaneous presence of smoking and other drugs, suboptimal nutritional status, and enhanced genetic susceptibility. Targeted animal models indicate developmental abnormalities in the number and migration of 5-HT neurons in the rostral domain that are associated with forebrain changes in 5-HT terminal innervation and 5-HT receptor and transporter binding that potentially contribute to the cognitive deficits of FASD (Druse *et al.*, 2006; Sari and Zhou, 2004; Tajuddin and Druse, 2001; Zafar *et al.*, 2000; Zhou *et al.*, 2005; Zhou *et al.*, 2001). Underappreciated clinically is that infants and children with FAS/D demonstrate impairments in cardiorespiratory function and state regulation in addition to cognitive and emotional deficits. These homeostatic impairments include abnormal tilt responses to blood pressure challenges (Fifer *et al.*, 2009), abnormal heart rate and heart rate variability (Fifer *et al.*, 2009), and poor sleep (Steinhausen *et al.*, 1993). Prenatal alcohol exposure in animal models results in: 1) reduced respiratory frequency and minute ventilation (Dubois *et al.*, 2006); 2) impaired respiratory adaptive responses to hypoxia (Dubois *et al.*, 2008; Kervern *et al.*, 2009); and 3) impaired phrenic nerve responses to ischemia (Dubois *et al.*, 2008). Recently an approximately 22% reduction in medullary raphé 5-HT neurons was reported in mice with prenatal alcohol exposure in association with reduced 5-HT neurons in the median and dorsal raphé (Zhou *et al.*, 2008), supporting the involvement of the caudal, as well as rostral, 5-HT domain in FASD. The human neuropathology of FASD includes microcephaly, migration disturbances, anomalies of the corpus callosum, and neuroimaging evidence of quantitative volume abnormalities in the cerebral cortex, basal ganglia, and cerebellum (Guerri *et al.*, 2009). A systemic study of 5-HT markers in the rostral and caudal domains in human FAS/D at autopsy has yet to be reported.

Maternal depression and selective serotonin reuptake (SSRI) use during pregnancy

During pregnancy, 10–15% of women in the United States suffer a major depressive disorder (Belik, 2008; Oberlander *et al.*, 2009; Oberlander *et al.*, 2006). Approximately 33% of antenatal depression is treated with SSRIs (Oberlander *et al.*, 2009). These drugs cross the placenta and fetal blood-brain-barrier (Belik, 2008; Oberlander *et al.*, 2009; Rampono *et al.*, 2009); cord blood demonstrates drug levels approximately 60% of maternal levels (Belik, 2008). While plasma 5-HT concentrations significantly increase after the injection of the SSRI fluoxetine in rats, prolonged exposure leads to decreased plasma and whole blood concentrations in humans and mice (Belik, 2008). The use of SSRIs during pregnancy is associated with neurobehavioral and gastrointestinal abnormalities in up to 30% of neonates that comprise a so-called “discontinuation syndrome” (Belik, 2008; Galbally *et al.*, 2009; Rampono *et al.*, 2009). This self-limited disorder is characterized by tremor, irritability, jitteriness, oxygen desaturation during feeding, restless sleep, increased or decreased tone, jaundice, hyperthermia, hypoglycemia, respiratory distress, and gastrointestinal symptoms (Belik, 2008; Chambers *et al.*, 1996; Galbally *et al.*, 2009). Its onset is from 2 days to 1 month following birth and it lasts less than 2 weeks (Belik, 2008). The disorder is likened to withdrawal rather than overt toxicity due to 5-HT excess (Belik, 2008; Haddad, 1998), and is associated with reduced levels of 5-HT and 5-HIAA in cord blood (Laine *et al.*, 2003). The widespread abnormalities of the SSRI discontinuance syndrome in state, autonomic, sensory, and motor regulation reflect the diffuse projections of the rostral and caudal 5-HT domains, yet autopsy studies analyzing these domains in affected human neonates are not available. The prominence of gastrointestinal signs also suggests dysfunction of the enteric 5-HT system. Due to the potential negative effects of SSRIs upon

the newborn, the Food and Drug administration provides warnings regarding their use during pregnancy (Belik, 2008).

The question arises, do altered levels of 5-HT in pregnant women—either possibly too low in the untreated depressed condition or too high in the treated condition with an SSRI—affect the development of the fetal brain at critical time-points in gestation, especially in light of 5-HT's trophic role in neuronal proliferation, migration, and differentiation? Maternal depression during pregnancy is associated with prematurity, low birth weight, altered state regulation, and impaired responsiveness to stimuli in the fetus and infant, as well as attention and neurobehavioral impairments in children (Field, 2011; Oberlander *et al.*, 2009). The consequences of untreated maternal stress upon fetal brain development are largely attributed to high maternal and fetal levels of cortisol and glucocorticoid receptor-mediated effects via the hypothalamic-pituitary-adrenal axis (Field, 2011; Oberlander *et al.*, 2009). Yet, 5-HT signaling is also directly affected by gestational stress. Such stress, for example, increases the levels of tryptophan, 5-HT, and 5-HIAA in the fetal rat brain until at least postnatal day 10, with reduced hippocampal 5-HT and increased 5-HIAA levels at postnatal day 35 (Oberlander *et al.*, 2009; Peters, 1990). Elevated 5-HT levels during gestation and immediately postnatally cause permanent axonal connection deficits in mice (Gaspar *et al.*, 2003). Neonatal SSRI exposure, on the other hand, is also associated with 5-HT abnormalities, as demonstrated in treated rats with neurobehavioral and 5-HT circuitry impairments lasting into adulthood, including alterations in 5-HT and TPH2 levels (Maciag *et al.*, 2006). Mice with genetically disrupted 5-HT transporter function, i.e., a model of SSRI exposure originating *in utero*, also display behavioral, neuroanatomic, and molecular abnormalities (Oberlander *et al.*, 2009), as well as impaired breathing and CO₂ responses (Li and Nattie, 2008; Penatti *et al.*, 2011). In fetal sheep the administration of gestational SSRIs is associated with altered breathing, rapid eye movement (REM) sleep, and electrical cortical activity (Morrison *et al.*, 2001). In sheep, the SSRI fluoxetine transiently reduces uterine blood (Morrison *et al.*, 2002), suggesting that fetal hypoxia contributes to neonatal SSRI toxicity. The long-term neurological consequences of prenatal SSRI exposure in humans are presently unknown (Oberlander *et al.*, 2009), particularly in regards to structural changes in the caudal and rostral 5-HT domains and/or their synaptic targets. The report of neurobehavioral abnormalities in exposed 4-year-olds with increased cord blood SSRI levels and history of neonatal discontinuance syndrome suggests the potential for long-lasting effects (Oberlander *et al.*, 2007).

Sudden infant death syndrome (SIDS)

The sudden infant death syndrome is the sudden death of an infant that remains unexplained by a complete autopsy, death scene investigation, and review of the clinical history (Willinger *et al.*, 1991). It is the leading cause of postneonatal infant mortality and the third cause of infant mortality in general in the United States today (Kinney and Thach, 2009). Death occurs either during sleep itself or one of the many spontaneous transitions to waking that occur throughout sleep (Kinney *et al.*, 2009). Typically, a seemingly healthy infant is found dead after the sleep period. Yet, substantial evidence suggests that SIDS infants are not entirely normal prior to death, but rather, have subclinical impairments in respiratory and/or autonomic control and arousal that define an underlying vulnerability and that appear to put them at risk for sudden death during a susceptible period, i.e., the first year of life (the period of risk for SIDS)(see review in (Kinney *et al.*, 2009)). Death during sleep in the vulnerable infant may be triggered by an exogenous stressor such as prone sleep position or face-down sleep position that leads to a homeostatic challenge, e.g., hypoxia, hypercarbia, or asphyxia, to which the infant cannot respond (Kinney *et al.*, 2009; Kinney and Thach, 2009). Monitor recordings of infants who subsequently die of SIDS indicate episodic apnea and bradycardia days and even weeks before death, indicating that the disease process is not

simply “agonal” (see reviews in (Kinney *et al.*, 2009; Kinney and Thach, 2009)). In addition, some infants who subsequently die of SIDS demonstrate subtle cardiorespiratory dysfunction at birth, as identified in large prospective studies (Kinney *et al.*, 2005; Kinney *et al.*, 2009; Kinney and Thach, 2009). The association of SIDS with risk factors related to gestation, e.g., maternal smoking and drinking during pregnancy (Fleming and Blair, 2007; Iyasu *et al.*, 2002; Kinney and Thach, 2009), suggests that SIDS originates *in utero* and leads to death in the vulnerable postnatal period.

Over the last two decades, our laboratory has defined a 5-HT disorder in the caudal 5-HT system in the majority of SIDS cases (Duncan *et al.*, 2010; Kinney *et al.*, 2003; Panigrahy *et al.*, 2000; Paterson *et al.*, 2006b). This disorder, delineated in 4 independent datasets, is characterized by significantly decreased levels of 5-HT (26% reduction) and TPH2 (22% reduction), in association with substantial alterations in 5-HT receptor and transporter binding and 5-HT neuronal density and maturation (Duncan *et al.*, 2010; Kinney *et al.*, 2003; Panigrahy *et al.*, 2000; Paterson *et al.*, 2006b). These abnormalities involve raphé, extra-raphé, and ventral (arcuate) populations comprised of 5-HT source neurons, as well as their projection sites, e.g., dorsal motor nucleus of the vagus, nucleus of the solitary tract. The reduced 5-HT levels are not associated with alterations in norepinephrine, dopamine, or their metabolites (Duncan *et al.*, 2010). Independent laboratories have also reported 5-HT related abnormalities in SIDS brainstems (Kopp *et al.*, 1994; Machaalani *et al.*, 2009; Ozawa and Okado, 2002; Waters, 2010). Moreover, increased 5-HIAA (as well as dopamine and noradrenergic metabolite) levels have been reported in the CSF of SIDS cases (Cann-Moisan *et al.*, 1999; Caroff *et al.*, 1992). The profile of abnormalities in 5-HT markers differs in SIDS cases from that in infants who die with chronic hypoxia, suggesting that hypoxia is not directly causative and that the 5-HT deficiency results from an as yet undefined primary cause (Duncan *et al.*, 2010; Panigrahy *et al.*, 2000). Nevertheless, the majority of SIDS deaths are associated with circumstances around the time of death that implicate hypoxia or asphyxia in the pathogenesis of death, e.g., face-down sleep position, soft bedding around the face, and bed sharing (Pasquale-Styles *et al.*, 2007). Based upon these findings, we propose that SIDS is deficiency of the medullary 5-HT system which causes an inability to restore homeostasis following life-threatening challenges, e.g., asphyxia, during a sleep period (possibly during sleep itself), leading to sudden death in the critical first year of life when homeostatic systems are still immature. While the most robust and reproducible neurotransmitter findings in SIDS brainstems relate to 5-HT, we and others have reported variable abnormalities in other neurotransmitter systems (see review in (Kinney *et al.*, 2009)). Thus, we hypothesize that SIDS is due to impaired homeostatic networks which involve the interplay between 5-HT and other related neurotransmitters and neuromodulators in the medulla. The report of an abnormal autonomic and respiratory profile detected prospectively at 2 days of life and associated with negligible 5-HT receptor binding in the medullary 5-HT system at autopsy in a two-week-old SIDS infant supports the link between SIDS, state-related (subclinical) cardiorespiratory impairments, and medullary 5-HT abnormalities (Fig. 11) (Kinney *et al.*, 2005).

The question arises, is SIDS a disorder exclusively of the caudal 5-HT domain or is the rostral 5-HT domain and/or its forebrain projection sites affected as well? In two reported studies of 5-HT receptor binding utilizing the broad radioligand ³H-LSD with tissue autoradiography, we analyzed nuclei throughout the entire brainstem, including in the median and dorsal raphé in the rostral pons and midbrain (Kinney *et al.*, 2003; Panigrahy *et al.*, 2000). In the same SIDS cases with medullary 5-HT receptor binding abnormalities, we found alterations in binding in the dorsal raphé but not the median raphé in the SIDS cases of one (American Indian) cohort (Kinney *et al.*, 2003), but no alterations in either the median or dorsal raphé in the second (non-American Indian) cohort (Panigrahy *et al.*, 2000)

The basis for this discrepancy is unclear but may reflect differences in the demographic and exposure features of the cohorts (Kinney *et al.*, 2003; Panigrahy *et al.*, 2000).

The risk factors for SIDS include maternal smoking and drinking during pregnancy, maternal depression, polymorphisms in 5-HT-related genes, and seemingly trivial infection around the time of death (see review (Kinney and Thach, 2009)). Each of these factors may potentially impact the pre- and/or postnatal development of the medullary 5-HT system. Nicotine in maternal cigarette smoke, for example, may bind to nAChRs on 5-HT neurons in the fetal medulla and adversely influence subsequent 5-HT neuronal development and/or functions. Our demonstration of transient high nicotinic receptor binding in the medullary 5-HT system of the human fetus at midgestation (Kinney *et al.*, 1993) indicates a site of a developmentally regulated interaction between nicotine and 5-HT neurons via nicotinic receptors. In this regard, fetal primates exposed to maternal nicotine display altered 5-HT_{1A} receptor binding, as well as altered nAChR binding, in the medullary raphe which is associated with autonomic dysfunction (Duncan *et al.*, 2009). Prenatal exposure to nicotine in rhesus monkeys also evokes elevations in brainstem 5-HT levels and turnover (Slotkin *et al.*, 2011). Thus, prenatal nicotine exposure may lead to 5-HT abnormalities, suggesting a biologic mechanism whereby maternal smoking during pregnancy is directly toxic to 5-HT metabolism, including in the caudal 5-HT domain. This possibility is supported by the finding that exposure to any smoking during pregnancy is associated with a 41% reduction in 5-HT receptor binding ($p=0.011$) in the human arcuate nucleus in the postnatal period (Kinney *et al.*, 2003). The adverse effects of prenatal alcohol exposure upon the development of the rostral and caudal 5-HT domains in animal models (see above) likewise provide plausibility for a biologic role for maternal drinking during pregnancy in the pathogenesis of medullary 5-HT pathology in affected SIDS infants. The rate of SIDS is significantly higher in mothers with postnatal depression (Mitchell *et al.*, 1992; Sanderson *et al.*, 2002), suggesting a potential interaction between maternal depressive vulnerability and impaired prenatal medullary 5-HT development. The relationship of prenatal SSRI exposure to SIDS is unknown. While polymorphisms in genes related to the 5-HT transporter promoter, MAO, TPH2, and 5-HT neuronal differentiation have been reported in SIDS cases (Broadbelt *et al.*, 2009; Filonzi *et al.*, 2009; Haas *et al.*, 2009; Narita *et al.*, 2001; Opdal *et al.*, 2008; Paterson *et al.*, 2010; Rand *et al.*, 2009; Rand *et al.*, 2007; Weese-Mayer *et al.*, 2003), the results are based in general upon small sample sizes and not always replicated in independent laboratories (Broadbelt *et al.*, 2009; Haas *et al.*, 2009; Paterson *et al.*, 2010). Mild infection around the time of death is present in approximately one-half of SIDS infants (Rognum *et al.*, 2009). The expression of IL-6 is elevated in the arcuate nucleus in SIDS infants (Rognum *et al.*, 2009) which may reflect a compensatory mechanism whereby defective arcuate 5-HT neurons require excessive cytokine stimulation to respond to infection-induced hypercapnia (Rognum *et al.*, 2009).

Conclusions

In conclusion, the caudal 5-HT system is a critical component of a medullary “homeostatic network” that is situated in close proximity with the major effector nuclei of respiratory control, upper airway reflexes, and the autonomic nervous system (Figs. 1 and 2). The critical developmental period of the human caudal 5-HT system extends over a protracted time-frame from the embryonic period at least through the first postnatal year, with different 5-HT markers changing with different spatiotemporal profiles. Consequently, different insults at single or multiple pre- and postnatal time-points will have differential effects upon the system's development, and ultimately upon functional outcomes in early life and beyond. This critical period corresponds to the transition of the fetus to the extrauterine environment and self-sustaining homeostasis.

In this review, we unify clinical 5-HT-related disorders of early life under the rubric of “developmental serotonopathies” that have not previously been considered together in this light (Fig. 10) (Table 1). These disorders are characterized by dominant (but not necessarily exclusive) defects in 5-HT metabolism which originate during gestation or soon after birth, and which are associated with a variety of genetic and/or environmental factors. Moreover, we provide a conceptualization of developmental serotonopathies as affecting predominately the rostral 5-HT domain, caudal 5-HT domain, or both domains (Table 1). Pinpointing the 5-HT defect to the rostral and/or caudal domains may provide important insight into underlying molecular factors, developmental mechanisms, and connectivity restricted to that particular domain. Of note, several developmental serotonopathies involving the caudal 5-HT domain are associated with sudden death in early life, including SIDS, PWS, and Rett Syndrome. The capability to diagnosis the developmental serotonopathies is ever increasing via identification of gene or enzymatic defects, and/or by measurements of blood and/or CSF levels of 5-HT metabolites. The compelling evidence for clinical improvement in certain serotonopathies with 5-HT-related replacement reinforces the need to define the fundamental basis of all such disorders.

Acknowledgments

This work was funded by the National Institute of Child Health and Development (R37-HD20991, PO1-HD036379, and P30-HD18655 [Developmental Disabilities Research Center, Children's Hospital Boston]), National Institute of Alcoholism and Alcohol Abuse (U01 HD045991-06), Evelyn Deborah Barrett Fellowship for SIDS Research (KGB), Marley J Cherella Fellowship for SIDS Research (IJR), CJ Foundation for SIDS Research, First Candle/SIDS Alliance, and CJ Murphy Foundation for Solving the Puzzle of SIDS. We appreciate the assistance of Drs. Micheal M. Myers and William Fifer in the preparation of Figure 11.

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Highlight

The caudal 5-HT system is a neural network involved in the regulation of homeostasis.

A critical period in the development of the human caudal 5-HT system extends from the embryonic period through the first year of infancy, and spans birth, i.e., the time-point when the fetus makes the transition to independent (non-placental) homeostatic control.

Several human diseases are associated with dysfunction of the caudal 5-HT system and clinical homeostatic imbalances.

Figure 1.

Schematic diagram of the caudal 5-HT system and its relationship to homeostatic regulation. This system: 1) receives sensory input about the internal milieu via the nucleus of the solitary tract (visceral sensory) in the autonomic nervous system, as well as its own chemo- and glucose receptors in close relationship to arteries and/or cerebrospinal fluid; 2) modulates adjustments to homeostatic stresses via its projections to the major medullary effector nuclei (HG, hypoglossal nucleus; NTS, nucleus of the solitary tract; DMX, dorsal motor nucleus of the vagus; preBöt, preBötzinger complex, Phr Nucl, phrenic nucleus in the cervical spinal cord; and IML, intermediolateral column in the thoracic spinal cord); 3) receives modulatory input itself from the hypothalamus other limbic forebrain sites relevant to sleep/wake cycle regulation and cardiorespiratory effects via receptor-mediated interactions with diverse neurotransmitters and neuromodulators; and 4) interfaces with the cytokine system which is critical to homeostasis in its mediation of “protective” sickness behaviors and cellular defenses against tissue damage. Abbreviations: O₂, oxygen, CO₂, carbon dioxide; temp, temperature; glc, glucose.

Figure 2.

Schematic diagram of the topography of the caudal 5-HT system in the human infant medulla. The 5-HT neurons are adjacent to effector nuclei of cardiorespiratory function (solid gray). The source 5-HT neurons are located in the raphé (blue) and extra-raphé (green), and along the ventral medullary surface in the arcuate nucleus (red). Each circle represents a 5-HT neuron in the infant medulla. Abbreviations: GC, gigantocellularis; PGCL, paragigantocellularis lateralis; nAm, nucleus ambiguus; preBöt, putative locus of the human preBötzinger complex; PIO, principal inferior olive; NTS, nucleus of the solitary tract; HG, hypoglossal nucleus; DMX, dorsal motor nucleus of the vagus. The numbers stand for the cranial nerves.

Figure 3.

Comparative neuroanatomy of the ventral surface of the medulla in the cat (left) versus human infant (right). The red neuronal clusters represent cytological and positional homologous neuronal sites between the human arcuate nucleus (hARC) and the cat (arcuate-like) sites (cARC) that are respiratory chemosensitive fields based upon physiological testing (Filiano *et al.*, 1990). Other homologous cell populations are the cCT (cat conterminalis-like) and hCT (human conterminalis), as well as thickened marginal glia (TMG). Abbreviations: RP, raphé pallidus; PYR, pyramid; HN, hypoglossal nucleus; NTS, nucleus of the solitary tract; hCT, human nucleus conterminalis; CN 12, cranial nerve 12. Scale bar=5 millimeters.

Figure 4. Immunostained 5-HT neurons extend ventrally from the region of the raphé pallidus (midline) (A) along the ventral surface of the pyramids (B) in the human infant medulla (Kinney *et al.*, 2007). Abbreviations: pyr, pyramid; VMS, ventral medullary surface. A. ×4, scale bar=200 microns. B. ×10, scale bar=80 microns.

Figure 5.

Three-dimensional view of the ventral surface of the medulla in the cat (A), rat (B), and human infant (C). The classical distribution of the ventrolateral respiratory chemosensitive zones (M, S, and L regions) are illustrated in the cat diagram (A). The relationship of 5-HT neurons (green) to the major arterial system of the medulla (red) is shown in the rat (B) (Bradley *et al.*, 2002). The topographic distribution of immunostained 5-HT neurons in the human infant medulla are shown in the raphé (blue) and extra-raphé (paragigantocellularis lateralis) (green), and ventral surface (arcuate nucleus) (red) (Kinney *et al.*, 2007). Similar 5-HT neuronal “columns” in the rostrocaudal axis are noted in the rat (B) and human infant (C) and are in a homologous lateral positions to the M, S, and L regions in the cat (A). See text.

Figure 6.

Computer-based graphic plots of the topography of 5-HT neurons in the developing human medulla (Kinney *et al.*, 2007). The time period spans from 7–8 gestational weeks to 6 postnatal months, i.e., a critical period in homeostatic maturation in early human life. Each circle represents a 5-HT neuron in the raphé (blue), extra-raphé, and ventral surface (red). The medullary sections (cross-section) are to scale. By 15–22 gestational weeks, the basic topography is adult-like.

Figure 7.

The developmental profile of 5-HT receptor binding with the broad radioligand ^3H -LSD based upon tissue receptor autoradiography in 8 medullary nuclei (Paterson *et al.*, 2004). In all sites sampled, there is a marked reduction in binding over the second half of gestation; binding is relatively uniform through infancy. Scale bar= 1 centimeter.

Figure 8.

Montage of computer-based images of autoradiograms for 5-HT receptors (5-HT_{1A} and 5-HT_{2A}) and transporter (5-HTT) in the human infant medulla at the mid- and rostral levels in the infant medulla at 2–3 postnatal months. The tissue sections are from normative infants without neurological disorders or neuropathologic findings at autopsy. Computer-generated plots of 5-HT neurons at this level are provided for reference. The receptor binding patterns for inter-relating systems are also shown, i.e., cholinergic nicotinic and GABA_A receptors. The binding levels of each computer-generated mosaic of the autoradiograms are scaled to the individual ligands and not across ligands. See text for description and references to methods. Abbreviations: Arc, arcuate nucleus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; nAm, nucleus ambiguus; preBöt, preBötzinger complex; ROb, raphe obscurus; NTS, nucleus of the solitary tract; HG, hypoglossal nucleus; DMX, dorsal motor nucleus of the vagus; PIO, principal inferior olive; LSD, lysergic acid diethylamide; Nic, nicotine; Epi, epibatidine; Cyt, cytosine; Bgt, α -bungarotoxin. The autoradiographic images were obtained from the laboratory's archives. Scale bar=5 millimeters.

Figure 9.

Expression of different receptors of key neurotransmitters (5-HT, GABA_A and acetylcholine [nicotinic receptors]) and cytokine (IL-6R) that interface with 5-HT neurons, as demonstrated with double-label immunocytochemistry in the raphé obscurus in the normative human infant medulla at 2–3 postnatal months. Scale bar=100 microns. See text.

Figure 10. Schematic diagram of 5-HT synthetic and degradative pathways, receptors, and transporter. The sites of the different defects in developmental serotonopathies involving the caudal 5-HT domain are indicated. See text.

Figure 11.

Decreased 5-HT receptor binding with ^3H -LSD in the arcuate nucleus (encircled in red oval) in a SIDS case who died at 2 postnatal weeks compared to two age-related controls (Control A and Control B) (Kinney *et al.*, 2005). This infant was studied prospectively with different parameters of central cardiorespiratory control at 2 days of life. The bottom three panels show the histograms and fitted normal curves for respiratory rate in active sleep, difference of heart rate between active and quiet sleep, and sustained change in beat-to-beat heart rate variability. The y-axis in each of the three graphs is the proportion of the subjects with a particular parameter. This infant had values for each of these parameters (red dot) that were outside the 10th percentile of values. Abbreviations: NTS, nucleus of the solitary tract; ION, inferior olivary nucleus; Arc, arcuate nucleus; br/min, breaths per minute; AS, active sleep; HR, heart rate; QS, quiet sleep; HRV, heart rate variability; %, percent.

Table 1

Human developmental serotonopathies as defined by predominate involvement of the caudal, rostral, or both 5-HT domains.

Disorders of the Caudal and Rostral 5-HT Domains
<ul style="list-style-type: none">• Inborn errors of 5-HT metabolism• Autism spectrum disorder (ASD)• Rett Syndrome• Fetal Alcohol Syndrome (FAS)• Neonatal SSRI Discontinuation Syndrome
Disorders Mainly of the Caudal 5-HT Domain
<ul style="list-style-type: none">• Prader-Willi Syndrome• Sudden Infant death syndrome (SIDS)
Disorders Mainly of the Rostral 5-HT Domain
<ul style="list-style-type: none">• Unknown