Serotonin Research and Sudden Infant Death Syndrome (SIDS): A Selected Annotated Bibliography


Recent studies have identified abnormalities in the development and function of medullary serotonin (5-HT) pathways in postmortem brain from sudden infant death syndrome (SIDS) cases, suggesting 5-HT-mediated dysregulation of the autonomic nervous system (ANS) in SIDS. The human fifth Ewing variant gene FEV is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of serotonergic neuronal phenotype. We hypothesized that variations of FEV may underlie abnormalities of the 5-HT system in SIDS cases and thus may be associated with SIDS risk. To elucidate the relationship between variation in FEV and SIDS, DNA was prepared from 96 African American and white SIDS cases and 96 gender- and ethnicity-matched controls. Standard sequencing and analysis of FEV revealed a heterozygous insertion mutation (IVS-191_190insA) upstream of the 5' exon 3 splice site occurring more frequently in SIDS cases (6/96) compared with controls (0/96; p = 0.01) and in the overall African American group (6/98) compared with the white group (0/94; p = 0.03). Identification of a variation in a gene responsible for 5-HT neuronal development, exclusively in a subset of African American SIDS cases in this cohort, may help explain both the observed abnormalities of this system in some SIDS cases and the ethnic disparity observed in SIDS.


Say M, Machaalani R, Waters K.A. **Changes in serotonergic receptors 1A and 2A in the piglet brainstem after intermittent hypercapnic hypoxia (IHH) and nicotine.** Brain Res. 2007 Mar 19; [Epub ahead of print]

We studied the effects of intermittent hypercapnic hypoxia (IHH) and/or nicotine on the immunoreactivity of serotonergic (5-HT) receptors 1A and 2A in the piglet brainstem. These exposures were developed to mimic two common risk factors for Sudden Infant Death Syndrome (SIDS); prone sleeping (IHH) and cigarette smoke exposure (nicotine). Immunoreactivity for 5-HT(1A)R and 5-HT(2A)R were studied in four nuclei of the caudal medulla. Three exposure groups were compared to controls (n=14): IHH (n=10), nicotine (n=14), and nicotine+IH (n=14). In control piglets, the immunoreactivity of 5-HT(1A)R was highest in the hypoglossal nucleus (XII), followed by inferior olivary nucleus (ION), nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagus (DMNV), whereas for 5-HT(2A)R, the immunoreactivity was highest in DMNV/NTS.
and then ION. Compared to controls, IHH reduced 5-HT(1A)R immunoreactivity in all studied nuclei (p<0.05) but had no effect on 5-HT(2A)R immunoreactivity. Nicotine reduced 5-HT(1A)R immunoreactivity in the DMNV, ION and NTS (p<0.001), and reduced 5-HT(2A)R immunoreactivity in DMNV/NTS (p<0.05). Nicotine+IHH reduced 5-HT(1A)R in DMNV, ION and NTS (p<0.001) but had no effect on 5-HT(2A)R immunoreactivity. Effects of nicotine on the DMNV were more significant in males compared to the females. These results show for the first time that IHH and/or nicotine can reduce 5-HT receptor immunoreactivity within functionally important nuclei of the piglet medulla. The findings support our hypothesis that 5-HT receptor abnormalities may be caused by postnatal exposures to clinically-relevant stimuli such as cigarette smoke exposure and/or prone sleeping.

Full text available: www.sciencedirect.com (not a U.S. government website)

Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC.

*Multiple serotonergic brainstem abnormalities in sudden infant death syndrome.*

JAMA. 2006 Nov 1; 296(17):2124-32.

Context: The serotonergic (5-hydroxytryptamine [5-HT]) neurons in the medulla oblongata project extensively to autonomic and respiratory nuclei in the brainstem and spinal cord and help regulate homeostatic function. Previously, abnormalities in 5-HT receptor binding in the medullae of infants dying from sudden infant death syndrome (SIDS) were identified, suggesting that medullary 5-HT dysfunction may be responsible for a subset of SIDS cases. Objective: To investigate cellular defects associated with altered 5-HT receptor binding in the 5-HT pathways of the medulla in SIDS cases. Design, Setting, and Participants: Frozen medullae from infants dying from SIDS (cases) or from causes other than SIDS (controls) were obtained from the San Diego Medical Examiner's office between 1997 and 2005. Markers of 5-HT function were compared between SIDS cases and controls, adjusted for postconceptional age and postmortem interval. The number of samples available for each analysis ranged from 16 to 31 for SIDS cases and 6 to 10 for controls. An exploratory analysis of the correlation between markers and 6 recognized risk factors for SIDS was performed. Main Outcome Measures: 5-HT neuron count and density, 5-HT(1A) receptor binding density, and 5-HT transporter (5-HTT) binding density in the medullary 5-HT system; correlation between these markers and 6 recognized risk factors for SIDS. Results: Compared with controls, SIDS cases had a significantly higher 5-HT neuron count (mean [SD], 148.04 [51.96] vs 72.56 [52.36] cells, respectively; P<.001) and 5-HT neuron density (P<.001), as well as a significantly lower density of 5-HT(1A) receptor binding sites (P<.01 for all 9 nuclei) in regions of the medulla involved in homeostatic function. The ratio of 5-HTT binding density to 5-HT neuron count in the medulla was significantly lower in SIDS cases compared with controls (mean [SD], 0.70 [0.33] vs 1.93 [1.25] fmol/mg, respectively; P = .001). Male SIDS cases had significantly lower 5-HT(1A) binding density in the raphe obscurus compared with female cases (mean [SD], 16.2 [2.0] vs 29.6 [16.5] fmol/mg, respectively; P = .04) or with male and female controls combined (mean [SD], 53.9 [19.8] fmol/mg; P = .005). No association was found between 5-HT neuron count or
density, 5-HT(1A) receptor binding density, or 5-HTT receptor binding density and other risk factors. Conclusions: Medullary 5-HT pathology in SIDS is more extensive than previously delineated, potentially including abnormal 5-HT neuron firing, synthesis, release, and clearance. This study also provides preliminary neurochemical evidence that may help explain the increased vulnerability of boys to SIDS.

Full-text available at: http://jama.ama-assn.org/


Acute inhibition of serotonergic (5-HT) neurons in the medullary raphe (MR) using a 5-HT(1A) receptor agonist had an age-dependent impact on the "CO(2) response" of piglets (33). Our present study explored the effect of chronic 5-HT neuron lesions in the MR and extra-raphe on the ventilatory response to hypercapnia and hypoxia in piglets, with possible implications on the role of 5-HT in the sudden infant death syndrome. We established four experimental groups. Group 1 (n = 11) did not undergo any treatment. Groups 2, 3, and 4 were injected with either vehicle or the neurotoxin 5,7-dihydroxytryptamine in the cisterna magna during the first week of life (group 2, n = 9; group 4, n = 11) or second week of life (group 3, n = 10). Ventilation was recorded in response to 5% CO(2) (all groups) and 12% O(2) (group 2) during wakefulness and sleep up to postnatal day 25. Surprisingly, the piglets did not reveal changes in their CO(2) sensitivity during early postnatal development. Overall, considerable lesions of 5-HT neurons (up to 65% decrease) in the MR and extra-raphe had no impact on the CO(2) response, regardless of injection time. Postlesion raphe plasticity could explain why we observed no effect. 5,7-Dihydroxytryptamine-treated males, however, did present a lower CO(2) response during sleep. Hypoxia significantly altered the frequency during sleep in lesioned piglets. Further studies are necessary to elucidate the role of plasticity, sex, and 5-HT abnormalities in sudden infant death syndrome.

Full-text available at: http://jap.physiology.org/current.shtml


This report presents a review of findings related to brainstem serotonergic (5-HT) abnormalities in a subset of SIDS cases. From 1990 to 2003, author and her colleagues published a series of reports concerning 6 neurotransmitter systems in step tissue sections of the same SIDS and control brainstems [5,10-15]. Our overall conclusion was that the 5-HT system in the medulla oblongata, i.e., the so-called medullary 5-HT system, is abnormal in at least 50% of SIDS cases [16]. We focused on brainstem systems involved...
in the control of respiration, autonomic function, sleep, and arousal because of an increasing body of prospective studies involving infants who subsequently died of SIDS that indicate subtle abnormalities in respiratory and/or autonomic control during sleep and arousal patterns before death [17-19]. Moreover, studies in normal preterm and term infants have indicated that the period of SIDS risk is associated with diminished arousal and altered respiratory and autonomic functions in the prone position or face-covered, supine position that potentially increase vulnerability to SIDS [20-25]. They used the technique of tissue receptor autoradiography in these studies because it allowed us to make precise neurochemical measurements in selected nuclei involved in respiratory and autonomic control, arousal, and sleep (Fig. 1). In addition, it allowed them to compare these measurements with those in nuclei not involved in cardiorespiratory control and arousal as an index of specificity to the postulated preferential involvement of homeostatic-related nuclei. We selected the analysis of receptor binding as a marker of neurotransmitter-related dysfunction as a "first pass" in determining possible brainstem regions and neurotransmitter systems involved in SIDS. This technique essentially allowed a survey of all brainstem regions neurochemically. Thus, it is a ideal method to target potential neurotransmitter abnormalities in SIDS, particularly because the cardiorespiratory- and arousal-related regions of interest were unremarkable with conventional histology, except for subtle gliosis in some sites.

Full-text available at: http://springerlink.metapress.com/content/1615-5742/

Kinney HC, Myers MM, Belliveau RA, Randall LL, Trachtenberg FL, Fingers ST, Youngman M, Habbe D, Fifer WP.
Subtle autonomic and respiratory dysfunction in sudden infant death syndrome associated with serotonergic brainstem abnormalities: A case report.

Sudden infant death syndrome (SIDS) is characterized by a sleep-related death in a seemingly healthy infant. Previously, we reported abnormalities in the serotonergic (5-HT) system of the medulla in SIDS cases in 2 independent datasets, including in the Northern Plains American Indians. The medullary 5-HT system is composed of 5-HT neurons in the raphe, extra-raphe, and arcuate nucleus at the ventral surface. This system is thought to modulate respiratory and autonomic function, and thus abnormalities within it could potentially lead to imbalances in sympathetic and parasympathetic tone. We report the case of a full-term American Indian boy who died of SIDS at 2 postnatal weeks, and who had subtle respiratory and autonomic dysfunction measured prospectively on the second postnatal day. Cardiorespiratory assessment of heart rate variability suggested that the ratio of parasympathetic to sympathetic tone was higher than normal in active sleep and lower than normal in quiet sleep in this case. At autopsy, arcuate nucleus hypoplasia and 5-HT receptor-binding abnormalities in the arcuate nucleus and other components of the medullary 5-HT system were found. This case suggests that medullary 5-HT system abnormalities may be able to be identified by such physiological tests before death. Replication of these findings in a large population may lead to the development of predictive cardiorespiratory assessment tools for future screening to identify infants with medullary 5-HT abnormalities and SIDS risk.
Opdal SH, Rognum TO.  
**The sudden infant death syndrome gene: Does it exist?**  

Background: Sudden infant death syndrome (SIDS) is in a difficult position between the legal and medical systems. In the United Kingdom, prosecutors have for years applied the simple rule that 1 unexpected death in a family is a tragedy, 2 are suspicious, and 3 are murder. However, it seems that the pendulum has now swung to the opposite extreme; mutations or polymorphisms with unclear biological significance are accepted in court as possible causes of death. This development makes research on genetic predisposing factors for SIDS increasingly important, from the standpoint of the legal protection of infants. The genetic component of sudden infant death can be divided into 2 categories, ie (1) mutations that give rise to genetic disorders that constitute the cause of death by themselves and (2) polymorphisms that might predispose infants to death in critical situations. Distinguishing between these 2 categories is essential, and cases in which a mutation causing a lethal genetic disorder is identified should be diagnosed not as SIDS but as explained death. Genetic Alterations that may Cause Sudden Infant Death: Deficiencies in fatty acid metabolism have been extensively studied in cases of SIDS, and by far the most well-investigated mutation is the A985G mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene, which is the most prevalent mutation causing MCAD deficiency. However, <1% of sudden infant death cases investigated have this mutation, and findings of biochemical profiles seen in specific fatty acid oxidation disorders in a number of such cases emphasize the importance of investigating fatty acid oxidation disorders other than MCAD deficiency. Severe acute hypoglycemia may cause sudden death among infants, but only rare novel polymorphisms have been found when key proteins involved in the regulation of blood glucose levels are investigated in cases of SIDS. The long QT syndrome (LQTS) is another inherited condition proposed as the cause of death in some cases of sudden infant death. The LQTS is caused by mutations in genes encoding cardiac ion channels, and mutations in the genes KVLQT1 and SCNA5 have been identified in cases initially diagnosed as SIDS, in addition to several polymorphisms in these 2 genes and in the HERG gene. In addition, genetic risk factors for thrombosis were investigated in a small number of SIDS cases; the study concluded that venous thrombosis is not a major cause of sudden infant death. Gene Polymorphisms That May Predispose Infants To Sudden Infant Death Under Certain Circumstances: Many SIDS victims have an activated immune system, which may indicate that they are vulnerable to simple infections. One reason for such vulnerability may be partial deletions of the complement component 4 gene. In cases of SIDS, an association between slight infections before death and partial deletions of the complement component 4 gene has been identified, which may indicate that this combination represents increased risk of sudden infant death. There have been a few studies investigating HLA-DR genotypes and SIDS, but no association has been demonstrated. The most common polymorphisms in the interleukin-10 (IL-10) gene promoter have been investigated in SIDS cases, and the ATA/ATA genotype has been reported to be associated with both SIDS and infectious
death. The findings may indicate that, in a given situation, an infant with an unfavorable IL-10 genotype may exhibit aberrant IL-10 production, and they confirm the assumption that genes involved in the immune system are of importance with respect to sudden unexpected infant death. Another gene that has been investigated is the serotonin transporter gene, and an association between the long alleles of this gene and SIDS has been demonstrated. Serotonin influences a broad range of physiologic systems, as well as the interactions between the immune and nervous systems, and findings of decreased serotonergic binding in parts of the brainstem, together with the findings in the serotonin transporter gene, may indicate that serotonin plays a regulatory role in SIDS. It has also been speculated that inadequate thermal regulation is involved in SIDS, but investigations of genes encoding heat-shock proteins and genes encoding proteins involved in lipolysis from brown adipose tissue have not found evidence of linkages between common polymorphisms in these genes and SIDS. A number of human diseases are attributable to mutations in mitochondrial DNA (mtDNA), and there are several reasons to think that mtDNA mutations also are involved in SIDS. Both a higher substitution frequency and a different substitution pattern in the HVR-I region of mtDNA have been reported in SIDS cases, compared with control cases. A number of coding region mtDNA mutations have also been reported, but many are found only in 1 or a few SIDS cases, and, to date, no predominant mtDNA mutation has been found to be associated with SIDS. Conclusions: All mutations giving rise to metabolic disorders known to be associated with life-threatening events are possible candidates for genes involved in cases of sudden infant death, either as a cause of death or as a predisposing factor. It is necessary to distinguish between lethal mutations leading to diseases such as MCAD and LQTS, and polymorphisms (for instance, in the IL-10 gene and mtDNA) that are normal gene variants but might be suboptimal in critical situations and thus predispose infants to sudden infant death. It is unlikely that one mutation or polymorphism is the predisposing factor in all SIDS cases. However, it is likely that there are "SIDS genes" operating as a polygenic inheritance predisposing infants to sudden infant death, in combination with environmental risk factors. For genetically predisposed infants, a combination of, for instance, a slight infection, a prone sleeping position, and a warm environment may trigger a vicious circle with a death mechanism, including hyperthermia, irregular breathing, hypoxemia, and defective autoresuscitation, eventually leading to severe hypoxia, coma, and death.

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Background: The sudden infant death syndrome (SIDS) is still the main cause of postneonatal infant death and its cause is still unknown. Recently, the medullary serotonergic network deficiency theory has been proposed and an association between SIDS and neuronal plasticity has also been suggested. The growth-associated phosphoprotein 43 (GAP43) is a marker of synaptic plasticity and is critical for normal
development of the serotonergic innervation. Therefore, the characteristics of GAP43-positive elements and their association with serotonergic neurons were here investigated in the brainstem of SIDS victims. Materials and Methods: The materials of this study included 26 cases of SIDS and 12 control cases. The brainstem material was collected and the immunohistochemistry of GAP43 and tryptophan hydroxylase (TrypH) carried out. The density of GAP43-positive neurons and dendrites and of TrypH-positive neurons were measured quantitatively. Nonparametric analyses of GAP43 between SIDS and non-SIDS and correlation analyses between GAP43 and TrypH were performed. RESULTS: No significant difference in GAP43-associated findings was found between SIDS and non-SIDS nor any significant correlation between GAP43-associated findings and TrypH-positive neurons. Conclusions: The results of this study were not in agreement with the association of GAP43 with SIDS and with serotonergic innervation in SIDS.

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Serotonergic receptors in the midbrain correlated with physiological data on sleep apnea in SIDS victims.

Background: Recently it has been reported that serotonin and related matters are associated with the sudden infant death syndrome (SIDS), which is still the main cause of postneonatal infant death. To further explore this claim, the correlation between serotonin receptors in the brainstem and sleep apnea in SIDS victims was investigated. Materials and Methods: Among 27,000 infants studied prospectively to characterize their sleep-wake behavior, 38 infants died under 6 months of age including 26 cases of SIDS. All the infants had been recorded during one night in a pediatric sleep laboratory some 3-12 weeks before death. The frequency and duration of sleep apnea were analyzed. Brainstem material was collected and immunohistochemistry on 5-hydroxy tryptamine 1A (5HT1A) receptor was carried out. The density of 5HT1A receptor-positive neurons was measured quantitatively. Nonparametric analysis of the density of 5HT1A receptor-positive neurons was carried out between SIDS and non-SIDS cases. Correlation analyses were performed between the density of 5HT1A receptor-positive neurons and the data on sleep apnea. Results: There was no correlation between the pathological data on 5HT1A receptors and the physiological data on sleep apnea in SIDS victims. Conclusions: No correlation between pathological findings of serotonin and physiological findings of sleep apnea were not in agreement with the association of sleep apnea in pathophysiology of SIDS.

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Sawaguchi T, Patricia F, Kadhim H, Groswasser J, Sottiaux M, Nishida H, Kahn A.
The correlation between serotonergic neurons in the brainstem and sleep apnea in SIDS victims.
Early Hum Dev. 2003 Dec; 75 Suppl: S31-40.
Background: In the Sudden Infant Death Syndrome (SIDS), a medullary serotonergic network deficiency theory has been proposed, amongst many other hypotheses. The correlation between serotonergic neurons or dendritic spines in the brainstem of SIDS and sleep apnea was investigated here. Materials and Methods: Twenty-seven thousand infants were studied prospectively to characterize their sleep-wake behavior. Of these, 38 infants died under 6 months of age, including 26 cases of SIDS. The frequency and duration of sleep apnea were analyzed. Brainstem material was collected and immunohistochemistry for tryptophan hydroxylase (TrypH) carried out. The density of TrypH-positive neurons was measured quantitatively. Correlation analyses were carried out between the TrypH-associated pathological data and the physiological data of sleep apnea. Results: One significant positive correlation between the density of TrypH-positive neurons in the dorsal raphe nucleus of the midbrain and the duration of central apnea (p=0.027) was found in SIDS victims. Conclusions: Some of serotonergic facts could be involved in the pathophysiology of SIDS.

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The rate of the sudden infant death syndrome (SIDS) among American Indian infants in the Northern Plains is almost 6 times higher than in U.S. white infants. In a study of infant mortality among Northern Plains Indians, we tested the hypothesis that receptor binding abnormalities to the neurotransmitter serotonin (5-HT) in SIDS cases, compared with autopsied controls, occur in regions of the medulla oblongata that contain 5-HT neurons and that are critical for the regulation of cardiorespiration and central chemosensitivity during sleep, i.e. the medullary 5-HT system. Tritiated-lysergic acid diethylamide binding to 5-HT(1A-D) and 5-HT2 receptors was measured in 19 brainstem nuclei in 23 SIDS and 6 control infants using tissue receptor autoradiography. Binding in the arcuate nucleus, a part of the medullary 5-HT system along the ventral surface, in the SIDS infants (mean age-adjusted binding 7.1 +/- 0.8 fmol/mg tissue, n = 23) was significantly lower than in controls (mean age-adjusted binding 13.1 +/- 1.6 fmol/mg tissue, n = 5) (p = 0.003). Binding also demonstrated significant diagnosis x age interactions (p < 0.04) in 4 other nuclei that are components of the 5-HT system. These data suggest that medullary 5-HT dysfunction can lead to sleep-related, sudden death in affected SIDS infants, and confirm the same binding abnormalities reported by us in a larger dataset of non-American Indian SIDS and control infants. This study also links 5-HT abnormalities in the arcuate nucleus with exposure to adverse prenatal exposures, i.e. cigarette smoking (p = 0.011) and alcohol (p = 0.075), during the periconceptional period or throughout pregnancy. Prenatal exposure to cigarette smoke and/or alcohol may contribute to abnormal fetal medullary 5-HT development in SIDS infants.
Serotonergic receptor binding in the arcuate nucleus, n. raphe obscurus, and other medullary regions is decreased in sudden infant death syndrome (SIDS) cases. Further, an insertion/deletion polymorphism in the promoter region of the serotonin transporter protein (5-HTT) gene has recently been associated with risk of SIDS. This polymorphism differentially regulates 5-HTT expression, with the long allele (L), the SIDS-associated allele, being a more effective promoter than the short allele (S). To further elucidate the role of the 5-HTT gene in SIDS, we investigated the 5-HTT intron 2 polymorphism, which also differentially regulates 5-HTT expression with the 12 repeat allele being the more effective promoter. In a cohort of 90 SIDS cases (44 African-American and 46 Caucasian) and gender/ethnicity-matched controls, significant positive associations were found between SIDS and the intron 2 genotype distribution (P-value = 0.041) among African-American SIDS vs. African-American controls, specifically with the 12/12 genotype (P-value = 0.03), and with the 12 repeat allele (P-value=0.018). The frequency of the 12/12 genotype and 12-repeat allele was significantly different (P < 0.001) between the African-American and Caucasian SIDS cases. Furthermore, the promoter and intron 2 loci were in significant linkage disequilibrium, and the L-12 haplotype was significantly associated with SIDS in the African-American (P = 0.002) but not Caucasian (P = 0.117) subgroups. These results indicate a relationship between SIDS and the 12-repeat allele of the intron 2 variable number tandem repeat of the 5-HTT gene in African-Americans, and a significant role of the haplotype containing the 12-repeat allele and the promoter L-allele in defining SIDS risk in African-Americans. These data, if confirmed in larger studies, may begin to explain the differences in SIDS incidence by ethnicity, suggest a role for levels of 5-HTT expression in generation of SIDS susceptibility, and provide an important tool for identifying at-risk individuals and estimating the risk of recurrence.


Serotonergic receptor binding in the arcuate nucleus, n. raphe obscurus, and other medullary regions is decreased in sudden infant death syndrome (SIDS) cases. Further, a variable tandem repeat sequence polymorphism in the promoter region of the serotonin transporter protein (5-HTT) gene has recently been associated with risk of SIDS in a Japanese cohort. This polymorphism differentially regulates 5-HTT expression, with the long allele (L), the SIDS-associated allele, being a more effective promoter than the short allele (S). We therefore investigated the 5-HTT promoter polymorphism in a cohort of 87

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SID S cases (43 African American and 44 Caucasian) and gender/ethnicity-matched controls. Significant positive associations were found between SIDS and the 5-HTT genotype distribution ($P = 0.022$), specifically with the L/L genotype ($P = 0.048$), and between SIDS and the 5-HTT L allele ($P = 0.005$). There was also a significant negative association between SIDS and the S/S genotype ($P = 0.011$). The comparisons were repeated in the African American and Caucasian subgroups. The data patterns were consistent in the subgroups, i.e., the L/L genotype and L allele were increased in the cases, but not all subgroup comparisons were statistically significant. These results indicate a relationship between SIDS and the L allele of the 5-HTT gene in African Americans and Caucasians, and if confirmed, will provide an important tool for identifying at-risk individuals and estimating the risk of recurrence.

Full-text available at: [http://www3.interscience.wiley.com](http://www3.interscience.wiley.com)


We compared the developmental changes of 5-hydroxytryptamine (5-HT) 1A and 5-HT2A receptor immunoreactivity in the nuclei in relation to the cardiorespiratory or autonomic function in the human brain stem in sudden infant death syndrome (SIDS) and congenital central hypoventilation syndrome (CCHS) patients and age-matched controls by means of immunohistochemical methods. There were significant decreases in 5-HT1A and 5-HT2A receptor immunoreactivity in the dorsal nucleus of the vagus, solitary nucleus and ventrolateral medulla in the medulla oblongata, and significant increases in the periaqueductal gray matter (PAG) of the midbrain in SIDS victims, but there were no significant differences between those in CCHS patients and controls. The decreased immunoreactivity of the receptors in the medulla oblongata was accompanied by brain stem gliosis. Therefore, the decreases in the receptors may be secondary to chronic hypoxia or repeated ischemia, but may be causally related to some impairment of the developing cardiorespiratory neuronal system. As 5-HT1A and 5-HT2A receptors were the most abundant in the fetal period and then decreased with subsequent development, the increases in 5-HT1A and 5-HT2A receptor immunoreactivity in PAG may reflect delayed neuronal maturation, but may also reflect compensatory changes in response to hypofunctioning serotonergic neurons in the medulla oblongata in SIDS. There was no abnormal expression of 5-HT1A and 5-HT2A receptors in CCHS brain stems, and so the pathophysiology seems to be different between SIDS and CCHS patients.

Full-text available at: [http://www.thieme.com/SID1993196364533/journals/pubid1432672485.html](http://www.thieme.com/SID1993196364533/journals/pubid1432672485.html)

We have previously shown that serotonergic neurons of the medulla are strongly stimulated by an increase in CO(2), suggesting that they are central respiratory chemoreceptors. Here we used confocal imaging and electron microscopy to show that neurons immunoreactive for tryptophan hydroxylase (TpOH) are tightly apposed to large arteries in the rat medulla. We used patch-clamp recordings from brain slices to confirm that neurons with this anatomical specialization are chemosensitive. Serotonergic neurons are ideally situated for sensing arterial blood CO(2), and may help maintain pH homeostasis via wide-ranging effects on brain function. The results reported here support a recent proposal that sudden infant death syndrome (SIDS) results from a developmental abnormality of medullary serotonergic neurons.

Full-text available at: [http://www.nature.com/neuro/index.html](http://www.nature.com/neuro/index.html)

Okado N, Narita M, Narita N.
**A serotonin malfunction hypothesis by finding clear mutual relationships between several risk factors and symptoms associated with sudden infant death syndrome.**

In our recent study allele variants in the promoter of serotonin transporter (5-HTT) gene have been shown as a novel risk factor for sudden infant death syndrome (SIDS). L and XL alleles were more frequent and S allele was less frequent in SIDS victims compared to age-matched controls. Serotonin (5-HT) is suggested as a major agent that is closely involved in the etiology of SIDS. Although many risk factors of SIDS looked mutually unrelated each other, we found in literature many of them other than prone position to change 5-HT levels in the brain. Along with the genetic factors, environmental and temporal factors appear additively to lower the excitatory function of 5-HT to the respiratory center, and finally SIDS might occur. Now the pathophysiological mechanisms and symptoms of SIDS are explained by decreased levels of 5-HT.


Richerson GB, Wang W, Tiwari J, Bradley SR.
**Chemosensitivity of serotonergic neurons in the rostral ventral medulla.**
Respir Physiol. 2001 Dec; 129(1-2):175-89.

The medullary raphe contains two subtypes of chemosensitive neuron: one that is stimulated by acidosis and another that is inhibited. Both types of neuron are putative chemoreceptors, proposed to act in opposite ways to modulate respiratory output and other pH sensitive brain functions. In this review, we will discuss the cellular properties of these chemosensitive raphe neurons when studied in vitro using brain slices and primary dissociated cell culture. Quantification of chemosensitivity of raphe neurons indicates that they are highly sensitive to small changes in extracellular pH (pH(o)) between 7.2 and 7.6. Stimulation by acidosis occurs only in the specific phenotypic subset of neurons within the raphe that are serotonergic. These serotonergic neurons also have other properties consistent with a specialized role in chemoreception. Homologous serotonergic neurons are present within the ventrolateral medulla (VLM), and may have
contributed to localization of respiratory chemoreception to that region. Chemosensitivity of raphe neurons increases in the postnatal period in rats, in parallel with development of respiratory chemoreception in vivo. An abnormality of serotonergic neurons of the ventral medulla has been identified in victims of sudden infant death syndrome (SIDS). The cellular properties of serotonergic raphe neurons suggest that they play a role in the CNS response to hypercapnia, and that they may contribute to interactions between the sleep/wake cycle and respiratory control.


Objective: Serotonin (5-HT) in the nervous system is a major factor in facilitation of the brain center for respiration. Variations in the promoter region of the 5-HT transporter (5-HTT) gene have been shown to potentially regulate 5-HT activity in the brain. Therefore, we aimed to identify the possibility that specific allele variants of the 5-HTT gene can be found as a genetic background for sudden infant death syndrome (SIDS). Methods: Polymorphisms in the 5' regulatory region of the 5-HTT gene were determined in genomic DNA obtained from 27 SIDS victims and 115 age-matched health control participants. Results: There were significant differences in genotype distribution and allele frequency of the 5-HTT promoter gene between SIDS victims and age-matched control participants. The L and XL alleles were more frequently found in SIDS victims than in age-matched control participants. Conclusion: Efficiency in the transportation of 5-HTT with the L allele is known to be higher than that with the S allele. The excitatory function by 5-HT is considered to be lower in the respiratory center of individuals with the L allele compared with those with S allele. The XL allele variant has shown another novel biological risk factor for SIDS.

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The sudden infant death syndrome (SIDS) is the leading cause of postneonatal infant mortality in the United States today, despite a dramatic 38% decrease in incidence due to a national risk reduction campaign advocating the supine sleep position. Our research in SIDS brains, beginning in 1985 and involving a single, large dataset, has become increasingly focused upon a specific neurotransmitter (serotonin) and specific territories (ventral medulla and regions of the medullary reticular formation that contain serotonergic neurons). Based on this research, we propose that SIDS, or a subset of SIDS, is due to a developmental abnormality in a medullary network composed of (at least in part) rhombic lip-derived, serotonergic neurons, including in the caudal raphe and arcuate nucleus (putative human homologue of the cat respiratory chemosensitive fields);
and this abnormality results in a failure of protective responses to life-threatening stressors (e.g. asphyxia, hypoxia, hypercapnia) during sleep as the infant passes through a critical period in homeostatic control. We call this the medullary serotonergic network deficiency hypothesis. We review the triple-risk model for SIDS, the development of the dataset using tissue autoradiography for analyzing neurotransmitter receptor binding; age-dependent baseline neurochemical findings in the human brainstem during early life; the evidence for serotonergic, rhombic lip, and ventral medullary deficits in at least some SIDS victim; possible mechanisms of sudden infant death related to these deficits; and potential causes of the deficits in the medullary serotonergic network in SIDS victims. We conclude with a summary of future directions in SIDS brainstem research.