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Reports

Sporadic Autonomic Dysregulation and Death Associated with Excessive Serotonin Autoinhibition

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Sudden infant death syndrome is the leading cause of death in the postneonatal period in developed countries. Postmortem studies show alterations in serotonin neurons in the brainstem of such infants. However, the mechanism by which altered serotonin homeostasis might cause sudden death is unknown. We investigated the consequences of altering the autoinhibitory capacity of serotonin neurons with the reversible overexpression of serotonin 1A autoreceptors in transgenic mice. Overexpressing mice exhibited sporadic bradycardia and hypothermia that occurred during a limited developmental period and frequently progressed to death. Moreover, overexpressing mice failed to activate autonomic target organs in response to environmental challenges. These findings show that excessive serotonin autoinhibition is a risk factor for catastrophic autonomic dysregulation and provide a mechanism for a role of altered serotonin homeostasis in sudden infant death syndrome.

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http://www.ncbi.nlm.nih.gov/pubmed/15908092

Prog Neuropsychopharmacol Biol Psychiatry. 2005 Jun;29(5):713-7.

A pilot genetic study of the continuum between compulsivity and impulsivity in females: the serotonin transporter promoter polymorphism.

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According to some authors the obsessive-compulsive (OC) spectrum includes on one extreme, the Obsessive-Compulsive Disorder (OCD) and on the other extreme the most impulsive behaviors. This is a controversial idea and other authors define the OC spectrum in different ways. The serotonin transporter (5-HTT) gene is one of the main genes that control serotonergic function. A polymorphism in the promoter area of this gene classifies subjects with low expression as S individuals (s/s or s/l) and subjects with high expression as L individuals (l/l). This polymorphism was studied in female OCD patients (n = 24), non-impulsive controls (n = 112) and impulsive suicidal patients (n = 118) to support the OC spectrum hypothesis from a genetic perspective. A linear association exists among the serotonin transporter promoter functional genotypes (S versus L individuals) (chi2 linear by linear association = 8.9; df = 1; p = 0.003). The frequency of S individuals (s/l or s/s) was lowest in OCD (54%, 13/24); intermediate in non-impulsive controls (71%, 80/112) and highest in impulsive suicide attempters (82%, 96/117). More importantly, future studies need to consider that genetics may be related to behavioral dimensions (compulsivity to impulsivity) instead of to specific psychiatric disorders defined in clinical terms.

Remark Ph. Hug : Instead of looking genetic problems (the trash of the actual science), just take a look on the EMF effects !

http://www.ncbi.nlm.nih.gov/pubmed/16603135

Biol Psychiatry. 2006 Sep 1;60(5):507-14. Epub 2006 Apr 5.

Tryptophan depletion affects heart rate variability and impulsivity in remitted depressed patients with a history of suicidal ideation.

Booij L, **Swenne CA**, **Brosschot JF**, **Haffmans PM**, **Thayer JF**, **Van der Does AJ**.

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BACKGROUND: Depression is a major risk factor for cardiovascular disease. An important risk factor for cardiovascular disease, low heart rate variability, often has been found in depressed patients and has been associated with impulsivity. The present study investigated whether experimental lowering of serotonin would decrease heart rate variability and increase impulsivity in remitted depressed patients, in particular in those patients with disturbed impulse control.

METHODS: Nineteen patients in remission from depression received high-dose and low-dose acute tryptophan depletion in a randomized, counterbalanced, double-blind crossover design. Heart rate variability and impulsivity were assessed during each acute tryptophan depletion session and during a baseline session. Suicidal ideation during past depression was used as an index for individual differences in impulse control.

RESULTS: High-dose acute tryptophan depletion led to a larger increase in depressive symptoms than did low-dose acute tryptophan depletion. High-dose acute tryptophan depletion decreased heart rate variability and increased impulsivity and anxiety, but only in patients with a history of suicidal ideation. Symptom effects of high-dose acute tryptophan depletion correlated with low heart rate variability at baseline.

CONCLUSIONS: **Depressed patients who have problems with controlling impulsivity might be more at risk for developing cardiovascular disease, possibly related to increased vulnerability to impaired 5-hydroxytryptamine function**.

http://www.ncbi.nlm.nih.gov/pubmed/1691169

J Clin Psychiatry. 1990 Apr;51 Suppl:31-41; discussion 42-3.

CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence.

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Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md 20892.

A neuroanatomical central nervous system (CNS) mechanism for the expression of emotions and behaviors in animals has now been proposed for over 50 years. More specifically, alterations in CNS serotonin associated with aggressive behavior in certain animal models have been among the most frequent, reliable, and replicable findings. Because alterations in CNS monoamines, i.e., catechols and indols, have been related to hypotheses for affective disorders and associated with both suicidal and aggressive behaviors, human clinical implications have emerged. The original studies, which reported an association between low cerebrospinal fluid 5-hydroxyindole-acetic acid concentration and impulsive, destructive behaviors, particularly where aggression and violence are involved, have now been replicated rather consistently in a number of countries and cultures.

Remark Ph. Hug : is it why we have more and more dogs and cows aggressive ? ? ?
Thanks to the EMF !

http://www.ncbi.nlm.nih.gov/pubmed/8559785

Physiol Behav. 1995 Oct;58(4):743-8.

Effects of electromagnetic fields and gender on neurotransmitters and amino acids in rats.

Chance WT, **Grossman CJ**, **Newrock R**, **Bovin G**, **Yerian S**, **Schmitt G**, **Mendenhall C**.

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Epidemiological studies have linked electromagnetic field (EMF) exposure to certain forms of cancer, however only limited laboratory evidence supports a connection between EMF and biological effects. In the present study we exposed male and female rats to low level, 1000 milli-Gauss (mGs), direct current EMF generated with Helmholtz coils for 1 mo or 4 mo. The effects of these EMF exposures on regional brain neurotransmitter metabolism and circulating amino acid concentrations were determined. After 1 mo of EMF exposure the concentration of serotonin was elevated in the hypothalamus of male rats. Levels of the dopamine metabolite, 3-methoxytyramine, were increased in the corpus striatum of male and female rats that were exposed to EMF for 1 mo. Hypothalamic concentration of norepinephrine was elevated in both groups of male rats, as compared to respective female groups, but was not affected by EMF. Similarly, levels of tyrosine were increased in hypothalamus, corpus striatum and nucleus accumbens of male rats, but were not affected by EMF exposure. Following 4 mo of EMF exposure, no significant effect of EMF was observed. Significant sex differences in plasma amino acid concentrations were observed in both studies, with female rats exhibiting decreases in a majority of the amino acids measured. These results are suggestive that short-term exposure may cause small alterations in neurotransmitter metabolism and in circulating amino acids, which dissipate when exposure duration is increased.

Remark Ph. Hug : 1000 milliGauss = 100 microTesla

http://www.ncbi.nlm.nih.gov/pubmed/15645480

Am J Med Genet C Semin Med Genet. 2005 Feb 15;133C(1):25-33.

Suicidal behavior: relationship between phenotype and serotonergic genotype.

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The basis of suicidal behavior (SB) is complex and multifactorial. Numerous risk factors have been identified. Epidemiological genetics studies (family studies, twin studies, adoption studies) suggest that there is a genetic basis to SB and that this genetic basis is specific and independent from the genetic factors implicated in predisposition to psychiatric disorders associated with SB (bipolar disorder, schizophrenia, alcoholism). Recently, new molecular genetics tools have been designed to identify the genetic factors that predispose certain individuals to disorders of complex etiology. Biological psychiatry studies have suggested that the physiopathology of SB involves dysfunctioning of the serotonin system. The first genetic association studies tested candidate genes encoding proteins involved in serotonin metabolism. The results of these studies suggest that the gene coding for the limiting enzyme in the synthesis of serotonin, tryptophan hydroxylase (TPH), and the gene encoding the serotonin transporter are involved in predisposition to SB. Furthermore, it is likely that these genes interact with each other and **with environmental factors** (early) and that they have different phenotypic consequences. One of the main aims of studies currently underway is to identify the precise phenotypes associated with genes that predispose to SB or intermediate phenotypes (impulsivity, inability to control anger, etc.).

Remark Ph. Hug : environmental factors = mmmmmmmh... like EMF ?

http://www.ncbi.nlm.nih.gov/pubmed/14706424

Biol Psychiatry. 2004 Jan 1;55(1):46-51.

Serotonin transporter gene may be involved in short-term risk of subsequent suicide attempts.

Courtet P, **Picot MC**, **Bellivier F**, **Torres S**, **Jollant F**, **Michelon C**, **Castelnau D**, **Astruc B**, **Buresi C**, **Malafosse A**.

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BACKGROUND: In the first year following a suicide attempt, patients are at high risk for reattempt and for completed suicide. We aim to determine the predictive value of two serotonin-related genes, the tryptophan hydroxylase (TPH) and serotonin transporter (5-HTTLPR) genes that have been involved in the susceptibility to suicidal behavior.

METHODS: After a one-year follow-up study of 103 patients hospitalized after a suicide attempt, patients have been genotyped for both the A218C TPH and the functional S/L 5-HTTLPR polymorphisms.

RESULTS: Patients who reattempted suicide during the follow-up period had significantly higher frequencies of the S allele and the SS genotype. The odds ratio for the SS genotype vs. the LL genotype was 6.5 (95% CI [1.18-35.84]). No difference was observed for TPH gene. Patients carrying the SS genotype were more impulsive. However, multivariate analysis suggested an independent effect of both the SS genotype and impulsivity on the risk of repeated suicide attempts.

CONCLUSIONS: These results suggest that the 5-HTTLPR SS genotype is associated with further suicide attempts among patients who have previously attempted suicide.

Remark Ph. Hug : is this gene exist since 50 generations or since we are exposed to EMF ?

http://www.ncbi.nlm.nih.gov/pubmed/15534946

J Psychiatry Neurosci. 2004 Sep;29(5):350-9.

[Implication of genes of the serotonergic system on vulnerability to suicidal behavior]

[Article in French]

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There are many risk factors associated with vulnerability to suicidal behaviour, and the results of family studies, twin studies and adoption studies suggest that they include a genetic predisposition. Moreover, this gentic susceptibility may be specific and independent of the genetic susceptibility to psychiatric disorders associated with suicidal behaviour (e.g., bipolar disorders, schizophrenia, alcoholism). Several groups have carried out association studies using a "candidate gene strategy", with the goal of identifying the genes involved in susceptibility to suicidal behavior. There is compelling evidence from research in biological psychiatry that abnormalities in the functioning of the central serotonergic system are involved in the pathogenesis of suicidal behavior, and the results of association studies suggest that the gene coding for tryptophan hydroxylase, which is the serotonin synthesis enzyme, and the serotonin transporter gene are involved in susceptibility to suicidal behavior. Furthermore, these genes may influence the suicidal phenotype through different gene-gene interactions and gene-early **environment** interactions. Current studies aim to identify either the precise phenotypes associated with genes for vulnerability to suicidal behaviour or the intermediate phenotypes (e.g., impulsivity, anger dyscontrol) associated with these genes.

Remark Ph. Hug : environment.....mmmmmmmh.....like EMF ? ? ?

http://www.ncbi.nlm.nih.gov/pubmed/12724937

Biomed Sci Instrum. 2003;39:466-70.

Autoradiographic evaluation of electromagnetic field effects on serotonin (5HT1A) receptors in rat brain.

Johnson MT, **McCullough J**, **Nindl G**, **Chamberlain JK**.

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Serotonin (5HT1A) is a chemical mediator of inflammation and the largest single neurotransmitter system of the brain. Its secretion and physiological actions mediate stress and pain, affecting both immune and nervous system functions through the hypothalamic-pituitary-adrenal axis. Serotonin receptor dysfunction is well-characterized in mental disturbances like depression and anxiety. Transcranial magnetic stimulation has been used therapeutically to treat refractory disorders like non-responsive depression and may act in part through its effect on 5HT1A receptors. **Previously we have shown that in vitro, 5HT1A receptor binding to a radioactive agonist can be modulated by specific intensity and frequency electromagnetic fields (EMFs)**. In the present report we have used quantitative receptor autoradiography to evaluate 5HT1A receptor density in rat brain and the impact of pulsed EMF exposure on receptor binding in key brain regions. Rats used in this study had whole body exposures to either a geofield control or to pulsed EMFs to evaluate the treatment for chemically-induced tendinitis. Since the brains were exposed coincidentally as a consequence of the main experiment, we investigated the potential for EMF-induced changes in areas such as the hippocampus. This pilot study should provide a detailed understanding of magnetic field effects on stress-responsive brain regions and will lead to a more coordinated approach to the use of such modalities for therapeutic intervention in humans.

Remark Ph. Hug : "approach therapeutic intervention"... well, what about the cause of EMF ?

http://www.ncbi.nlm.nih.gov/pubmed/18055084

Prog Neuropsychopharmacol Biol Psychiatry. 2008 Feb 15;32(2):544-51. Epub 2007 Oct 30.

Platelet serotonin concentration and suicidal behavior in combat related posttraumatic stress disorder.

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Posttraumatic stress disorder (PTSD) is a serious and global problem, a psychiatric disorder that frequently occurs with different comorbidities, and is associated with a high suicide rate. Pathophysiologically, both PTSD and suicidal behavior are related to disturbances in the central serotonergic system. **Serotonin (5-hydroxytryptamine, 5-HT) controls emotional behavior, anxiety, impulsivity and aggression, and nearly all known antidepressants and antianxiety drugs affect 5-HT transmission**. Platelet 5-HT can be used as a limited peripheral marker of the central serotonergic synaptosomes, since it is related to particular basic psychopathological characteristics of several psychiatric disorders. Platelet 5-HT concentration has been reported to be similar in PTSD subjects and healthy controls, but suicidal patients across different psychiatric diagnoses have reduced platelet 5-HT concentration. This study examined platelet 5-HT concentration by the spectrofluorimetric method in male subjects: 73 suicidal and 47 non-suicidal veterans with current and chronic combat related PTSD, 45 suicidal and 30 non-suicidal comparative non-PTSD subjects and 147 healthy men. The presence of suicidal behavior (score=0, non-suicidal; scores > or =1, suicidal) was assessed with the Hamilton Depression Rating Scale-17 (HDRS). Platelet 5-HT concentration was significantly lower in suicidal PTSD and non-PTSD patients compared to non-suicidal patients or healthy controls. Since the majority of patients scored very low on item 3 of HDRS, no significant correlation between suicidal scores and platelet 5-HT concentration was found. These results show that reduced platelet 5-HT concentration is related to suicidal behavior in PTSD, and suggest that platelet 5-HT concentration might be used as a peripheral marker to predict suicidal behavior across psychiatric diagnoses.

Remark Ph. Hug : are the psychiatrics able to diagnose that EMF effects are the source of the problem ?

http://www.ncbi.nlm.nih.gov/pubmed/1693500

Biochem Biophys Res Commun. 1990 May 31;169(1):102-8.

Marked rapid alterations in nocturnal pineal serotonin metabolism in mice and rats exposed to weak intermittent magnetic fields.

Lerchl A, **Nonaka KO**, **Stokkan KA**, **Reiter RJ**.

Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio 78284-7762.

Adult AMES mice and male Sprague Dawley rats were exposed to an artificial magnetic field, generated by Helmholtz coils. 3.5 hours after the onset of darkness the coils were activated for one hour resulting in an inversion of the horizontal component of the earth's magnetic field. The coils were activated and deactivated at 5 min intervals during the 1 hour exposure period. In both mice and rats, the levels of serotonin in the pineal were markedly increased by the exposure. In rats, an increase of pineal 5-hydroxyindole acetic acid and a decrease of the activity of the pineal enzyme serotonin-N-acetyltransferase also was observed. However, pineal and serum melatonin levels were not altered. The results indicate that the metabolism of serotonin in the pineal is quickly affected by the exposure of animals to a magnetic field.

http://www.ncbi.nlm.nih.gov/pubmed/15163439

Eur Neuropsychopharmacol. 2004 Aug;14(4):295-300.

Impulsivity related to brain serotonin transporter binding capacity in suicide attempters.

Lindström MB, **Ryding E**, **Bosson P**, **Ahnlide JA**, **Rosén I**, **Träskman-Bendz L**.

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Altered monoaminergic activity has earlier been associated with violent suicidal behaviour. In this study whole brain binding potential of the serotonin transporter (5HTT) and dopamine transporter (DAT) was measured by single photon emission computerised tomography (SPECT) in 12 patients after a serious suicide attempt and in 12 age, sex and season matched healthy controls. Clinical and temperamental assessments were analysed for possible associations with 5HTT and DAT. We found no significant 5HTT or DAT differences between patients and controls. In patients, but not in controls, there was a significant correlation between whole brain 5HTT and DAT. Impulsiveness according to the Marke Nyman Temperament (MNT) was significantly correlated to 5HTT in suicide attempters, but not in controls. Neither of the transporters could be regarded as a marker for serious suicidal behaviour. A previously discussed connection between serotonin and dopamine was replicated in this study. In suicide attempters, low 5HTT was associated with impulsivity and to some extent with depressive disorder-key factors for suicidal behaviour.

http://www.ncbi.nlm.nih.gov/pubmed/2697011

Psychopharmacol Bull. 1989;25(3):407-13.

Neurochemical studies of violent and nonviolent suicide.

Mann JJ, **Marzuk PM**, **Arango V**, **McBride PA**, **Leon AC**, **Tierney H**.

Considerable data have been reported indicating that there is a relationship between suicide or more serious suicide attempts and alterations in indices of serotonin (5-HT) function in patients. The fact that these data are based on studies of both suicide completers as well as more serious suicide attempters and involve a range of experimental techniques spanning biochemical assays of postmortem brain tissue as well as neuroendocrine challenge tests and platelet studies strengthens this finding. However, whether altered serotonin indices are specifically associated with violent compared to nonviolent suicide remains less clear. The relationship may be with some other aspect of suicidal behavior such as the overall lethality of the suicide method, impulsivity, or degree of planning. Suicide method appears to be related to modeling effects or to the relative availability of different methods of suicide, which argues against a predominant role for biological factors in selecting suicide methods. The relative importance of biological vs. modeling and sociological factors in determining suicide method will require more comprehensive studies in which the contribution of all of these factors is assessed simultaneously in the same patient population.

http://www.ncbi.nlm.nih.gov/pubmed/11282247

Neuropsychopharmacology. 2001 May;24(5):467-77.

The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system.

Mann JJ, **Brent DA**, **Arango V**.

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Numerous abnormalities have been found in the serotonergic system in suicide attempters and completers. There is considerable evidence that the serotonergic system is partly under genetic control and that as yet unknown genetic factors mediate the risk for suicidal behavior independently of the genetic factors responsible for the heritability of major psychiatric conditions associated with suicide. An argument is made that there is a relationship of genetic variants to intermediate phenotypes, such as impulsivity, psychomotor change, pathological aggression and biological abnormalities including specific gene products. A variety of biological indices have been generated by new approaches using postmortem tissue and in vivo imaging that will provide a rich substrate for further genetic studies.

Remark Ph. Hug : "rich substrate for further genetic studies" mmmmmmmmmh.... not the matter what is the cause (EMF). Give money for more studies...

http://www.ncbi.nlm.nih.gov/pubmed/7506517

Arch Gen Psychiatry. 1994 Jan;51(1):34-8.

Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism.

Nielsen DA, **Goldman D**, **Virkkunen M**, **Tokola R**, **Rawlings R**, **Linnoila M**.

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BACKGROUND: To examine whether the tryptophan hydroxylase (TPH) gene, which codes for the rate-limiting enzyme in the biosynthesis of serotonin, may be a factor influencing serotonin turnover and behaviors controlled by serotonin.

METHODS: Using a polymerase chain reaction-based method, TPH genotype was determined in DNA samples from 56 impulsive and 14 nonimpulsive, alcoholic, violent offenders and 20 healthy volunteers.

RESULTS: In the behaviorally extreme impulsive group, we observed a significant association between TPH genotype and cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) concentration. No association of TPH genotype with impulsive behavior was detected. The polymorphism was also associated with a history of suicide attempts in all violent offenders, independent of impulsivity status and cerebrospinal fluid 5-HIAA concentration.

CONCLUSION: In some individuals, a genetic variant of the TPH gene may influence 5-HIAA concentration in the cerebrospinal fluid and predisposition to suicidal behavior.

http://www.ncbi.nlm.nih.gov/pubmed/10729928

Psychiatr Clin North Am. 2000 Mar;23(1):11-25.

The biology of impulsivity and suicidality.

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Abnormalities of 5-HT and noradrenergic functioning have been implicated in aggressive impulsivity, SIB, and suicidal behavior. The role of DA and GABA in human studies of these behaviors requires further investigation. Most studies suggest that impulsive aggression is related to lower levels of CNS 5-HT. Some studies demonstrate that increasing NE correlates to impulsive aggression, whereas other studies demonstrate an opposite relationship. The role of NE in impulsive aggressive behavior is still unclear. Self-injurious behavior is similar to impulsive aggression in that it seems to be mediated by the neurotransmitter systems previously mentioned. For example, the presence of lower levels of 5-HT and abnormalities in the DA system are related to SIB in patients with BPD and depression. SIB severity also seems to be influenced by neglect (e.g., severe isolation during rearing). As animal studies suggest, increasing the amount of isolation and an earlier onset of isolation increase the severity of SIB. Suicidal behaviors and the lethality of suicide attempts may also be linked to the abnormalities in neurotransmitter systems similar to those found in patients with impulsive aggression and SIB, namely, lowered 5-HT transmission and enhanced DA and NE functioning. Understanding the biological triggers of impulsive aggression or SIB may allow for the evaluation of suicidal attempts and completion from a different perspective and, in conjunction with genetic predictors, may eventually help with the early prediction and prevention of suicidal behaviors. Additional studies of live subjects and postmortem brains will assist in clarifying the neurobiology of suicidal behaviors that are common to many disorders and are clinically relevant to BPD.

http://www.ncbi.nlm.nih.gov/pubmed/12655305

Neuropsychopharmacology. 2003 Apr;28(4):613-9. Epub 2002 Oct 17.

Serotonin transporter: a potential substrate in the biology of suicide.

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Suicide is a serious public health problem in the US, yet its neurobiological underpinnings are poorly understood. Suicide is highly correlated with depressive symptoms, and considerable evidence suggests that depression is associated with a relative deficiency in serotonergic neurotransmission. Serotonergic circuits also mediate impulsivity, a trait obviously relevant to suicide. These findings, taken together, suggest that alterations in the serotonergic system might contribute to suicidal behavior, serving as an impetus for researchers to scrutinize the serotonin transporter (SERT) as a potential substrate for the pathophysiology of suicide. Using post-mortem brain tissue, platelets, and DNA from suicide completers and attempters have not provided unequivocal evidence for a pre-eminent role for the SERT in the pathophysiology of suicide. This paper provides a review of several studies that have evaluated the role of the SERT in the pathophysiology of suicide.

http://www.ncbi.nlm.nih.gov/pubmed/16307979

Environ Res. 2005 Nov;99(3):369-77.

The effect of extremely low-frequency electromagnetic fields on skin and thyroid amine- and peptide-containing cells in rats: an immunohistochemical and morphometrical study.

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The aim of this study was to investigate the influence of extremely low-frequency electromagnetic fields (ELF-EMFs) on mast cells (MCs), parafollicular cells, and nerve fibers in rat skin and thyroid gland. The experiment was performed on 24 2-month-old Wistar male rats exposed for 4h a day, 7 days a week for 1 month to EMFs (50 Hz, 100-300 microT, 54-160 V/m). After sacrifice, samples of skin and thyroid were processed for indirect immunohistochemistry or toluidine blue staining and then were analyzed using the methods of stereology. The antibody markers to serotonin, substance P, calcitonin gene-related peptide (CGRP), and protein gene product 9.5 (PGP) were applied to skin sections and PGP, CGRP, and neuropeptide Y (NPY) markers to the thyroid. A significantly increased number of serotonin-positive MCs in the skin and NPY-containing nerve fibers in the thyroid of rats exposed to ELF-EMF was found compared to controls, indicating a possible EMF effect on skin and thyroid vasculature.

http://www.ncbi.nlm.nih.gov/pubmed/8098713

J Cell Biochem. 1993 Apr;51(4):394-403.

Static and extremely low frequency electromagnetic field exposure: reported effects on the circadian production of melatonin.

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The circadian rhythm of melatonin production (high melatonin levels at night and low during the day) in the mammalian pineal gland is modified by visible portions of the electromagnetic spectrum, i.e., light, and reportedly by extremely low frequency (ELF) electromagnetic fields as well as by static magnetic field exposure. Both light and non-visible electromagnetic field exposure at night depress the conversion of serotonin (5HT) to melatonin within the pineal gland. Several reports over the last decade showed that the chronic exposure of rats to a 60 Hz electric field, over a range of field strengths, severely attenuated the nighttime rise in pineal melatonin production; however, more recent studies have not confirmed this initial observation. Sinusoidal magnetic field exposure also has been shown to interfere with the nocturnal melatonin forming ability of the pineal gland although the number of studies using these field exposures is small. On the other hand, static magnetic fields have been repeatedly shown to perturb the circadian melatonin rhythm. The field strengths in these studies were almost always in the geomagnetic range (0.2 to 0.7 Gauss or 20 to 70 mu tesla) and most often the experimental animals were subjected either to a partial rotation or to a total inversion of the horizontal component of the geomagnetic field. These experiments showed that several parameters in the indole cascade in the pineal gland are modified by these field exposures; thus, pineal cyclic AMP levels, N-acetyltransferase (NAT) activity (the rate limiting enzyme in pineal melatonin production), hydroxyindole-O-methyltransferase (HIOMT) activity (the melatonin forming enzyme), and pineal and blood melatonin concentrations were depressed in various studies. Likewise, increases in pineal levels of 5HT and 5-hydroxyindole acetic acid (5HIAA) were also seen in these glands; these increases are consistent with a depressed melatonin synthesis. **The mechanisms whereby non-visible electromagnetic fields influence the melatonin forming ability of the pineal gland remain unknown**; however, the retinas in particular have been theorized to serve as magnetoreceptors with the altered melatonin cycle being a consequence of a disturbance in the neural biological clock, i.e., the suprachiasmatic nuclei (SCN) of the hypothalamus, which generates the circadian melatonin rhythm. **The disturbances in pineal melatonin production induced by either light exposure or non-visible electromagnetic field exposure at night appear to be the same but whether the underlying mechanisms are similar remains unknown**.

Remark Ph. Hug : when there is a FACT, why do we have to wait for an explanation of mechanisms before taking action ?

http://www.ncbi.nlm.nih.gov/pubmed/1382609

Biochim Biophys Acta. 1992 Oct 6;1137(1):59-64.

Pulsed static magnetic field effects on in-vitro pineal indoleamine metabolism.

Richardson BA, **Yaga K**, **Reiter RJ**, **Morton DJ**.

Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio 78284-7762.

In-vitro rat pineal glands stimulated with the beta-adrenergic receptor agonist isoproterenol to induce melatonin synthesis and exposed for 1 h to a pulsed 0.4-G static magnetic field demonstrated significant inhibition of serotonin-N-acetyltransferase activity and melatonin content. 2-h exposure to pulsed magnetic field also resulted in a significant reduction in isoproterenol-induced serotonin-N-acetyltransferase activity. **These results support the idea that the cultured pineal gland can be affected directly by artificially generated weak magnetic fields**.

Remark Ph. Hug : well, so we are supposed to know that since 1992...

http://www.ncbi.nlm.nih.gov/pubmed/7744555

Int J Neurosci. 1994 Nov;79(1-2):99-110.

A drug naive parkinsonian patient successfully treated with weak electromagnetic fields.

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Brief cerebral application of picotesla (pT) electromagnetic fields (EMF) has been demonstrated an efficacious, revolutionary treatment modality for the therapy of Parkinson's disease (PD) with clinical benefits being evident in all motor aspects of the disease as well as in nonmotor symptoms such as mood, sleep, pain, sexual dysfunction, autonomic regulation and cognitive functions. Since treatment with pT EMF has involved PD patients who were treated with dopaminergic agents at the time they received EMF there may have been a synergistic interaction between dopaminergic drugs and EMF. The present communication concerns a 49-year-old male Parkinsonian patient with stage 3 disability on the Hoehn and Yahr scale (1967) who, in response to brief extracranial applications of pT EMF, demonstrated a marked improvement in motor, depressive symptomatology and cognitive functions and was classified as stage 1 several weeks later. This case is remarkable in that the patient did not receive treatment with dopaminergic drugs prior to or during the course of EMF therapy. It suggests that (a) pT range EMF may be efficacious as a monotherapy for PD and should be considered also as a treatment modality for de novo diagnosed patients, and (b) application of these EMF improves Parkinsonism by a mechanism which involves, among others, augmentation of dopaminergic and serotonergic neurotransmission.

Remark Ph. Hug : Ha haaa ! So picoTesla could be good and ICNIRP, OMS, Governments are denied the bad effects of stronger, but legal, exposition ? ? ?

http://www.ncbi.nlm.nih.gov/pubmed/10984915

Zh Vyssh Nerv Deiat Im I P Pavlova. 2000 Jul-Aug;50(4):703-15.

[Species specificity, age factors, and various neurochemical correlates of the animal spontaneous behavior after exposure to electromagnetic field of the ultralow intensity]

[Article in Russian]

Shtemberg AS, **Uzbekov MG**, **Shikhov SN**, **Bazian AS**, **Cherniakov GM**.

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Behavioral and neurochemical reactions of small laboratory animals (mice and rats of different age) under exposure to ultralow-intensity electromagnetic fields (EMF, frequency of 4200 and 970 MHz, modulated by a quasistochastic signal in the range of 20-20,000 Hz, power density 15 microW/cm2, specific body absorption rate up to 4.5 mJ/kg) were studied. The EMF basically inhibited the locomotor and exploratory activity in the "open-field" test. The species- and age-specific features rather than radiation conditions dominated. However, decrease in the EMF frequency considerably intensified the observed effect. Change in animal behavior was accompanied by shifts in neurochemical processes, i.e., sharp activation of serotoninergic and inhibition of morepinephrinergic system.

http://www.ncbi.nlm.nih.gov/pubmed/17448449

Biol Psychiatry. 2007 Sep 15;62(6):580-7. Epub 2007 Apr 19.

5HT2A receptor binding is increased in borderline personality disorder.

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BACKGROUND: Postmortem studies in suicide victims demonstrate an increase in the number of post-synaptic 5-HT(2A) receptor binding sites in ventral lateral and orbital frontal cortex. Diminished metabolic responses to serotonergic activation are noted in these areas in impulsive subjects with borderline personality disorder (BPD), a group at high risk for suicidal behaviors. We examined 5HT(2A) receptor binding potential (BP) in impulsive subjects with BPD, with positron emission tomography neuroimaging with [(18)F] altanserin.

METHODS: Fourteen female subjects with BPD were assessed for Axis I comorbidity, depressed mood, impulsivity, aggression, suicidality, childhood abuse, and compared with 11 healthy female control subjects. The 5HT(2A) receptor binding was evaluated in prefrontal cortex, anterior cingulate, hippocampus, temporal lobe, occipital cortex, and thalamus. Data were analyzed with Logan graphical analysis and a four-compartment (4C) model.

RESULTS: Hippocampal 5HT(2A) receptor binding was significantly increased in BPD subjects compared with control subjects in both Logan and 4C analyses, covarying for age. Hippocampal BP values were related to comorbid major depressive episode, with highest values found in non-depressed BPD subjects and lowest in healthy control subjects. The BP values were not related to depressed mood, impulsivity, aggression, suicidality, or childhood abuse.

CONCLUSIONS: 5HT(2A) receptor binding is increased in the hippocampus of BPD subjects independent of depressed mood, impulsivity, aggression, suicidality, or childhood abuse. Dysregulation of serotonergic function in hippocampus might contribute to affective and behavioral symptoms in BPD.

Remark Ph. Hug : about conclusions : isn't it exactly what our society is living today in 2008 ?

http://www.ncbi.nlm.nih.gov/pubmed/9809241

Encephale. 1998 Jul-Aug;24(4):355-64.

[Heredity and role of serotonin in aggressive impulsive behavior]

[Article in French]

Staner L, **Mendlewicz J**.

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The idea that heredity could influence behaviour, including personality is very old. Until the early 1980s, the evidence for genetic influences on personality derived almost exclusively from twin studies. More recently, studies comparing twins raised together with those raised in different environment confirmed that about 40% of the observed personality variance can be attributable to genetic factors. Since complex behaviours, such as those underlying personality functioning, are likely to be influenced by many genes, a continuum of genetic risk underlying behavioural dimensions that extend from normal to abnormal behaviour has been hypothesized. Behaviours related to aggressive impulses regulation could delineate a biologically anchored model of dispositions to both normal and pathological functioning: these behaviours are identified in animal species where they are genetically transmitted, and a growing body of evidence suggests that disturbances in the regulation of aggressive impulses could belong to a behavioural dimension (disturbances of impulse control) linked to serotonin. Theorists involved in modelling personality according to psychobiologic basis agree with the idea of an inhibitory function of serotonin on impulsive behaviour and recognise that the way individuals control their impulses could underlie a basic psychobiological personality dimension. According to genotypes and to environmental factors, these serotonin mediated behaviours may be diversely expressed varying from minor personality peculiarities (characterised by impulsivity, hostility, irritability, psychopathic deviance, excessive violence or by more clear-cut personality dysfunctioning such as antisocial, borderline, narcissistic and histrionic personality traits or disorders) to major psychiatric disturbances (suicidal behaviour, overt aggressive behaviour, intermittent explosive disorder, pathological gambling, pyromania, bulimia and some type of substance or alcohol abuse). Finally, recent molecular genetic studies have demonstrated that genes encoding some key proteins involved in serotonin transmission could present some polymorphism in relation with impulsive-aggressive behaviours.

Remark Ph. Hug : this could explain this new phenomena : the "botellones" kind of collective buverie (drinking bout).

http://www.ncbi.nlm.nih.gov/pubmed/10739421

Am J Psychiatry. 2000 Apr;157(4):609-14.

Comment in:
Am J Psychiatry. 2001 Aug;158(8):1335-6.

Association of aggressive behavior with altered serotonergic function in patients who are not suicidal.

Stanley B, **Molcho A**, **Stanley M**, **Winchel R**, **Gameroff MJ**, **Parsons B**, **Mann JJ**.

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OBJECTIVE: The purpose of this study was to determine whether aggression and serotonergic dysfunction are related in the absence of a history of suicidal behavior. Although serotonergic dysfunction has been implicated in aggressive and impulsive behavior, most studies of such behavior have included individuals with a history of suicide attempts. Low concentrations of CSF 5-hydroxyindoleacetic acid (5-HIAA) have been consistently associated with suicidal behavior, presenting a potential confound in the link between aggression and serotonergic dysfunction.

METHOD: The authors examined the association between aggression and CSF 5-HIAA concentrations in a group of 64 patients who had different DSM-III-R axis I diagnoses and no past suicidal behavior. Aggressive (N=35) and nonaggressive (N=29) groups were defined by a median split on a six-item history of adulthood aggressive behavior.

RESULTS: The aggressive group had significantly lower CSF 5-HIAA concentrations than the nonaggressive group. Aggressive individuals also scored significantly higher on self-report measures of hostility, impulsiveness, and sensation seeking. CSF 5-HIAA concentrations, however, did not correlate with self-reported hostility and impulsivity.

CONCLUSIONS: There is an association between aggressive behavior and serotonergic dysfunction independent of suicidal behavior in patients with axis I disorders who exhibit relatively milder forms of aggressive behavior. Analogous to findings with suicidal behavior, a low concentration of CSF 5-HIAA is related to aggressive behavior but does not show the same relationship to the continuum of aggressive feelings and thoughts.

Remark Ph. Hug : well, EMF provoke serotonergic dysfunction which can reach from aggressive behavior to kill someone. Do a court admit that ? ? ?

http://www.ncbi.nlm.nih.gov/pubmed/16076550

Eur Neuropsychopharmacol. 2006 Jan;16(1):49-57. Epub 2005 Aug 1.

Plasma serotonin levels and suicidal behavior in adolescents.

Tyano S, **Zalsman G**, **Ofek H**, **Blum I**, **Apter A**, **Wolovik L**, **Sher L**, **Sommerfeld E**, **Harell D**, **Weizman A**.

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To evaluate the relationship between plasma serotonin (p5-HT) levels and psychometric measures in suicidal adolescents vs. controls, 211 adolescents from three sites in Israel were divided into four groups: suicidal psychiatric inpatients (n=35); non-suicidal psychiatric inpatients (n=30); adolescents referred to the emergency room (ER) due to a suicide attempt (n=51); and a community-based control group from 4 high schools in the same catchment areas (n=95). All were interviewed and assessed for violence, aggression, depression, impulsivity, anger, anxiety, and p5-HT. p5-HT levels were significantly lower in the control group compared to all other groups. A significant negative correlation was found between p5-HT level and suicidal behavior severity among the suicidal inpatients. p5-HT did not discriminate between the psychiatric diagnostic categories and was significantly lower in ER violent compared to non-violent subjects. Gender, depression, and anger were associated with suicidal behavior in all four groups. Beck Depression Inventory (BDI) scores together with p5-HT levels discriminated between healthy controls and other groups. p5-HT level in combination with some of the psychometric scales may serve as a safe and inexpensive peripheral marker of psychopathology, and may help to differentiate between sub-populations of suicidal adolescents. The biological mechanism behind the serotonin dysregulation in suicidal adolescents requires further investigation.

Remark Ph. Hug : ...”requires further investigations”. Well, how many people have to dye before we take action against EMF ?

http://www.ncbi.nlm.nih.gov/pubmed/11727896

Crisis. 2001;22(2):66-70.

Comment in:
Crisis. 2001;22(2):43-6.

Suicide, serotonin, and the brain.

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The involvement of impaired serotonergic functioning in the development of suicidal behavior is one of the best documented findings in biological psychiatry. It is, however, less clear in which way this dysfunction contributes to the occurrence of suicidal behavior. Correlational studies have demonstrated associations between peripheral measures of serotonergic function and characteristics such as impulsivity, disinhibition, anxiety, and/or behavioral inhibition. Postmortem and neuroimaging studies have provided insight in the localization of serotonergic dysfunction in the central nervous system. Nevertheless, results in this area of research have also been contradictory. Following a short overview of recent research findings on serotonin and suicidal behavior, this paper focuses on the involvement of the prefrontal cortex of the brain in the development of suicidal behavior and on the role of serotonin in its executive functions. Based on these considerations, suggestions for future research are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/6641877

Exp Brain Res. 1983;50(2-3):426-32.

Effects of an artificial magnetic field on serotonin N-acetyltransferase activity and melatonin content of the rat pineal gland.

Welker HA, **Semm P**, **Willig RP**, **Commentz JC**, **Wiltschko W**, **Vollrath L**.

In the present study the effects of artificial magnetic fields on pineal serotonin-N-acetyltransferase (NAT) activity and melatonin content in male Sprague-Dawley rats were investigated to study the secretory activity of the pineal gland. Experimental inversion of the horizontal component of the natural magnetic field, performed at night-time, led to a significant decrease of both parameters investigated. During day-time, this effect was less conspicuous. During night-time, inversion of the horizontal component is followed by a reduced pineal secretory activity for about 2 h. After 24 h exposure to the inverted horizontal component, return to the natural condition was followed by a renewed clear depression of pineal NAT activity and melatonin content, indicating that the main stimulus is not the inverted magnetic field itself but rather its change. Changing the inclination of the local magnetic field from 63 degrees to 58 degrees, 68 degrees or 78 degrees, respectively also decreased the secretory activity of the rat pineal gland.

Remark Ph. Hug : Nice experiment in.....1983 ! ! !
What a loosing time before taking action !

http://www.ncbi.nlm.nih.gov/pubmed/3288221

Bioelectromagnetics. 1988;9(2):195-205.

Chronic exposure to ELF fields may induce depression.

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Exposure to extremely-low-frequency (ELF) electric or magnetic fields has been postulated as a potentially contributing factor in depression. Epidemiologic studies have yielded positive correlations between magnetic- and/or electric-field strengths in local environments and the incidence of depression-related suicide. **Chronic exposure to ELF electric or magnetic fields can disrupt normal circadian rhythms in rat pineal serotonin-N-acetyltransferase activity as well as in serotonin and melatonin concentrations**. Such disruptions in the circadian rhythmicity of pineal melatonin secretion have been associated with certain depressive disorders in human beings. In the rat, ELF fields may interfere with tonic aspects of neuronal input to the pineal gland, giving rise to what may be termed "functional pinealectomy." If long-term exposure to ELF fields causes pineal dysfunction in human beings as it does in the rat, such dysfunction may contribute to the onset of depression or may exacerbate existing depressive disorders.

Remark Ph. Hug : Nice warning in 1988 ! ! !

http://www.ncbi.nlm.nih.gov/pubmed/11353442

Am J Med Genet. 2001 Apr 8;105(3):239-45.

Family-based association study of serotonin transporter promoter in suicidal adolescents: no association with suicidality but possible role in violence traits.

Zalsman G, **Frisch A**, **Bromberg M**, **Gelernter J**, **Michaelovsky E**, **Campino A**, **Erlich Z**, **Tyano S**, **Apter A**, **Weizman A**.

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The serotonin transporter-linked promoter region polymorphism (5-HTTLPR) is thought to be associated with some serotonin dysfunction-related psychopathologies such as depression and anxiety disorders. Suicide and suicide-related behaviors such as violence, aggression, and impulsivity have been reproducibly associated with serotonin dysfunction and are partially genetic. This study examined the association of 5-HTTLPR with suicidal behavior and related traits in Israeli suicidal adolescent inpatients using the haplotype relative risk (HRR) method that controls for artifacts caused by population stratification. Forty-eight inpatient adolescents who recently attempted suicide were assessed by structured interviews for detailed clinical history, diagnoses, suicide intent, suicide risk, impulsivity, violence, and depression. Blood samples were collected and DNA extracted from patients and their biological parents. The 5-HTTLPR allele frequencies were tested for association with suicidality by the HRR method. In addition, the relationship between genotypes and phenotypic severity of several clinical parameters was analyzed. No significant allelic association of the 5-HTTLPR polymorphism with suicidal behavior was found (chi square = 0.023; P = 0.88). Analysis of variance of the suicide-related trait measures for the three genotypes demonstrated a significant difference in violence measures between patients carrying the LL and LS genotypes (9.50+/-4.04 vs. 5.36+/-4.03; P = 0.029). This study suggests that the 5-HTTLPR polymorphism is unlikely to have major relevance to the pathogenesis of suicidal behavior in adolescence but may contribute to violent behavior in this population.

Some articles about sudden death

Archive for Saturday, July 05, 2008

Study suggests serotonin plays a role in SIDS

http://articles.latimes.com/2008/jul/05/science/sci-sids5

Mice who overproduced the brain chemical showed symptoms similar to those of the infant syndrome before they died.

By Wendy Hansen
July 05, 2008

Mice genetically engineered to overproduce the brain chemical serotonin died at an early age after developing symptoms similar to those of sudden infant death syndrome, suggesting improper regulation of serotonin may cause SIDS in humans.

The majority of the mice died after being unable to regulate their heart rate and body temperature, scientists reported Friday in the journal Science.

Dr. Cornelius Gross, a study author and head of the project at the European Molecular Biology Laboratory in Monterotondo, Italy, said the work might prompt clinical research "to devise diagnostic tests to try to identify those kids most likely to … die of SIDS."

SIDS is a condition in which seemingly healthy babies between 1 month and 1 year old die without warning or explanation. It kills approximately 2,700 infants in the U.S. each year.

The mice were part of a study on serotonin's role in aggression and anxiety, but after they began dying, a scientist suggested the deaths might be related to SIDS.

"This was a chance discovery," Gross said.

Serotonin, in addition to affecting mood, regulates bodily functions such as temperature, respiration and heart rate.

The findings support autopsy-based results reported from 2006 in which researchers from Children's Hospital Boston, led by Dr. Hannah Kinney, found that infants who died of SIDS had abnormal serotonin-producing cells in their brain stems.

Although differences exist between the mice and babies who die of SIDS, both reports point to improper regulation of the serotonin system as a cause of the disorder, the researchers said.

"The main impact is if you produce a very specific deficit in the serotonin system, you get a disastrous result," said Dr. Gene Nattie, a professor of physiology at Dartmouth Medical School, who worked with Kinney. "That's why the paper is important. It's certainly a big step forward."

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SIDS-like symptoms in mice with serotonin signaling defects

By John Timmer | Published: July 03, 2008 - 12:59PM CT
http://arstechnica.com/journals/science.ars/2008/07/03/sids-like-symptoms-in-mice-with-serotonin-signaling-defects

Sudden Infant Death Syndrome, or SIDS, is an extremely challenging thing to study. For years, it wasn't even clear whether the deaths of infants with no apparent abnormalities represented a distinct biological phenomenon. Over time, however, monitoring of infants revealed unexplained lapses in their regulation of

body temperature and heart rate, and postmortem examinations suggested an association with defective signaling involving the neurotransmitter serotonin. Now, researchers exploring serotonin signaling in mice may have created the first animal model of SIDS; a description will appear in today's issue of *Science*.

It's not at all clear that SIDS was what the group were after, since serotonin is involved in a wide variety of neural process, and its signaling pathway is the focus of a lot of drug development. Still, if chance favors the prepared mind, the researchers appear to have been very well prepared.

Their work focused on creating a mouse strain where the activity of the serotonin pathway could be manipulated experimentally. To do so, they used the *Htr1a* receptor, which helps tone down serotonin signaling. When this receptor binds the neurotransmitter, it actually inhibits the function of other receptors, producing a net decrease in serotonin signaling. The authors placed the *Htr1a* gene under the control of regulatory proteins such that it would normally be expressed, but administration of a drug called tetracycline would shut the gene down; for the purposes of this discussion we'll call that genetic construct Tet-*Htr1a*.

Mice that completely lack the *Htr1a* gene are fully viable, and those with the Tet-*Htr1a* combination were born in the expected number. But the majority of the mice died during the first few months after birth; by four months, roughly 70 percent of them were dead. Mortality rates returned to normal after this point, and the death could be completely suppressed by the administration of tetracycline, linking it directly to the gene.

The researchers started monitoring the mice, and found what they termed "sporadic autonomic crises" occurred in most of the Tet-*Htr1a* animals. These involved several hours in which body temperature was dysregulated, producing hypothermia; these periods also saw incidents of severe bradycardia. About 40 percent of the time, the mice did not recover, and died.

The authors argue that this provides a useful model of human SIDS, as serotonin signaling influences the function of the autonomic nervous system, which controls the activity of things like breath and heart rate. Serotonin signaling is also active during changes between sleep and wake states, which may explain the frequency of SIDS events associated with sleep. They do, however, recognize that the parallels are not exact; the mice involved are actually sexually mature during the time the deaths occur. Still, it's far better than not having a way to study the phenomenon at all.

Science, 2008. DOI: 10.1126/science.1157871

Science: Leading Cause of Infant Death Explained by Serotonin Receptor

http://www.aaas.org/news/releases/2008/0703sids.shtml

New research in *Science* provides a specific biological mechanism for Sudden Infant Death Syndrome (SIDS), providing new insight into a lethal and unpredictable affliction that claims the lives of about 2500 seemingly healthy infants every year in the United States.

Until now, biological risk factors have been difficult to pinpoint. Dysfunction of the brain transmitter serotonin was believed to trigger SIDS, but no one really knew how. A report in the 5 July issue of *Science* shows that a particular serotonin receptor creates faulty serotonin signaling and is enough to cause death in a mouse model of SIDS.

Risk factors for SIDS include sleeping stomach-down and overheating during sleep.

Low serotonin has been long been suspected as a risk factor but no mechanism for the deficiency had ever been identified. Enrica Audero—a postdoctoral fellow at the European Molecular Biology Laboratory in Monterotondo, Italy—and her colleagues investigated how over-expression of a serotonin receptor triggered serotonin dysfunction and frequently led to death in mice.

The researchers focused on the serotonin 1a receptor, a protein on nerve cells that works with serotonin to send chemical messages. Serotonin 1a receptors are autoreceptors—they can turn off serotonin if too much is released, much as how a thermostat senses and responds to temperature. Nerve cells that produce serotonin are clustered in the brainstem, which regulates basic body

functions including heart rate and breathing.

Other studies have found that activating serotonin 1a receptors leads to less firing of serotonin-containing nerve cells and decreases in heart rate, body temperature and respiration—which are also physiological factors contributing to SIDS.

Audero and her colleagues engineered transgenic mice with about 10 times more serotonin 1a receptor protein compared to their healthy, control littermates. When spritzed with tryptophan—a precursor for serotonin—brain slices from mice with serotonin1a receptor over-expression showed less cell-firing than control mice. The plunge in firing rate was evident within a few minutes of applying tryptophan; it was as if over-expressing serotonin 1a receptors led to an exaggerated shut-off of cells containing serotonin. If the researchers added a drug that blocked the serotonin 1a receptor, tryptophan was able to restore cell-firing. The finding demonstrates that the serotonin 1a receptor was causing the serotonin shut-off.

The researchers were simply looking for how serotonin feeds back on itself, when they began to realize that their engineered mice could be a model for SIDS.

"The majority of mice died suddenly early in their life," Cornelius Gross, senior author on the *Science* paper and researcher at the European Molecular Biology Laboratory, said during a AAAS/*Science* teleconference. Gross said the deaths were surprising because mice with genetic modifications to other parts of the serotonin signaling pathway do not die. The researchers looked at what was happening to the serotonin 1a over-expressing animals just before death, and they found a "dramatic drop" in heart rate and body temperature, Gross said.

At least one drop in heart rate and body temperature—called "sporadic autonomic crisis"—occurred in 73% of the serotonin 1a over-expressing mice. It took these animals hours and sometimes days to recover. In 37% of the transgenic mice, the crisis was so severe that the animals died.

"The events that precipitated crises in our animals are not known, and thus far we have not been able to identify environmental stressors that induce crises," wrote Audero and colleagues in *Science*. "However, we speculate that crises may occur preferentially after rapid changes in serotonin neuron activity." Such activities could occur during sleep-wake cycles.

The authors caution that their results may not directly explain SIDS, because SIDS infants do not show greater serotonin 1a receptors. But, it is possible that other "functionally equivalent deficits" in serotonin signaling may be at play.

Because the findings suggest that SIDS arises from abnormal brain development, the study could provide comfort to parents of babies who have died from SIDS. "I think it says to parents that their babies had a developmental disorder that they were born with," Marian Willinger, SIDS expert at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, said during a AAAS/*Science* teleconference on 3 July. SIDS babies are typically found dead in their cribs in the morning, frequently leading parents to blame themselves.

Willinger said that having an infant die of SIDS is a "devastating event" for a family. The *Science* study "should provide them with some sense of comfort that there was nothing they could have done to prevent it—it is a real disease," she said.

Brandon Bryn and Molly McElroy
3 July 2008