BOOK REVIEW

Genomic Imprinting and Neurodevelopmental Disorders of Sleep:

By Patrick McNamara, Ph.D.

INTRODUCTION

Many classical neurodevelopmental disorders such as autism, Down syndrome, attention deficit disorder, schizophrenia, Prader-Willi syndrome and many others are associated with dramatic sleep disturbances. A recent volume edited by Wiggs and Stores reviews sleep disturbances associated with a number of developmental disorders. The production of this text constitutes a real service to the sleep sciences as it has become clear that the nature and functions of sleep may be related to its role in development. Pharmacologic suppression of REM early in life, for example, will prevent normal development of brain structure and function. Pharmacologic suppression of REM in the adult even for months at a time, on the other hand, appears to have few if any negative effects. The second book under review here, by David Haig, on genomic imprinting covers a topic that may be less familiar to sleep scientists. Genomic imprinting refers to sets of genes inherited in non-Mendelian fashion depending on parent of origin (see below). Many imprinted genes appear to have a profound impact on mammalian development-including central nervous system (CNS) development. Haig is an evolutionary biologist who has developed the kinship or conflict theory of genomic imprinting that, to date, has been fairly successful in accounting for properties and functions of many imprinted genes. As predicted by Haig's theory, many imprinted genes act in an antagonistic fashion to either promote early growth if the gene is paternally expressed or inhibit/moderate growth rates if maternally expressed. Given that sleep biology is intimately involved in modulation of growth factors, such as growth hormone (GH), it may be that imprinting effects extend to the neurobiology of sleep states. If so, then we may use the molecular and theoretical tools used to understand imprinting to help us understand selected aspects of neurodevelopmental disorders of sleep. Better understanding of these disorders may, in turn, lead to new and better treatment options.

The first few chapters of the Stores and Wiggs text are written by the editors themselves and cover the basics of developmental sleep medicine. Each chapter is brief, to the point, and filled with useful tables and information. The material on selected developmental disorders commences in Part II of the volume with a chapter on sleep and Down syndrome by Rebecca Stores. Roughly half of these children exhibit sleep difficulties with more severe disturbances associated with greater intellectual impairment. The rest of the volume is taken up with descriptions of a variety of developmental

"Sleep disturbance in children and adolescents with disorders of development. Clinics in Developmental Medicine, 155," Edited by G Stores and L. Wiggs, Mac Keith Press, Cambridge University Press, London 2001, 221 pages; and of "Genomic imprinting and kinship" by D. Haig, Rutgers University Press, New Brunswick, New Jersey, 2002, 219 pages.

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Address reprint requests to: Patrick McNamara, Ph.D., Department of Neurology (127), VA New England Healthcare System, 150 South Huntington Avenue, Boston, MA 02130; email: mcnamar@bu.edu

Table 1. Potential Effects of imprinted genes on sleep.

CHROMOSOMAL IMPRINTING REGION 11p15.1-5		
Gene	**Expression**	**Effects**
DRD4	Limbic forebrain, possibly maternal transmission	Linked to ADHD; high novelty-seeking personality; ANS dysfunction 13-bp deletion of bases 235-267
Tyrosine hydroxylase		Rate-limiting enzyme for synthesis of catecholamines
GF2	Paternal	Mediates effects of IGF1 and growth hormone; promotes growth; GH and IGF1 promote NREM
BWS (Beckwith-Wiedemann syndrome)	Duplication of paternal copy of IGF2	Somatic overgrowth, sleep disturbances
Insulin (INS)	Paternally expressed in mouse yolk sac; paternal transmission of class I VNTR allele predisposes to childhood obesity	Stimulates/enhances NREM
CCK beta receptor		CCK stimulates both REM and NREM
CDKN1C P57K1P2	Maternal	Linked to Ondine's Curse (sleep related hypoventilation and SIDS) ? inhibitor of cyclin-dependant kinases
CHROMOSOMAL IMPRINTING REGION 15q11-q13		
Gene	**Expression**	**Effects**
PWS	Paternal (failure to express paternal) Maternal UPD	Hypersomnia/SOREM, REM fragmentation
AS	Maternal (fail to express)	Insomnia, night wakings
Autism Susceptible (AUTS)		Insomnia ?assoc RBD, linked to GABRB3
GABRB3	?conflicting maternal	GABA receptors influence both REM and NREM sleep onset processes
UBE3A	Maternal (failure to express – AS)	Via hippocampus
CHROMOSOMAL IMPRINTING REGION 20q13.2		
Gene	**Expression**	**Effects**
GNAS1 Gs-Alpha XL-alphaS NESP55	 Maternal Paternal Maternal	 Expressed in Pituitary Varient of G Protein subunit Neuroendocrine secretary protein 55
Melanocortin 3 receptor	?	POML-CLIP stimulates REM expressed in hypothalamus, partitions fuel stores into fat. Energy homeostasis
Congenital failure of autonomic control, central hypoventalation syndrome, Ondine's Curse	?	The patient breathes normally while awake but hypoventilates during REM
CHRNA4, Ach receptor nicotinic	?	Expressed in frontal cortex
Nocturnal FL epilepsy	?	Seizures in FL during NREM sleep may be linked to mutilations in CHRNA4 gene
Low voltage EEG (loss of alpha)	?	Increased sleepiness
Franken et al. for SWS delta QTL	?	Increased SWS delta power QTL at mouse ch2 homologous to 20q13.2
SEROTONIN		
Gene	**Expression**	**Effects**
5HT2AR (13q14-q21)	Maternal Limbic, prefrontal	* 5HT2 receptor antagonists enhance SWS; therefore normal action of these receptors must be to inhibit SWS * 5HT2A receptors in LDT/PPT regions may mediate inhibition of REM-on cells. Blockade of 5HT2A receptors in LDT/PPT enhance REM indices

and neurodevelopmental disorders with associated sleep disturbances. Prevalence of sleep disorders in the neurodevelopmental syndromes in particular is quite high and they exact a huge toll on the resources, both financial and emotional, of the families who care for the afflicted child. It is difficult to imagine how to adequately cope with a child with autism or with Angelmann syndrome who may go without sleep for days on end! Can a parent or guardian remain awake to look after the child for days on end as well? Children who exhibit excessive daytime sleepiness like those with Prader-Willi syndrome (Chapter 9 written by Vela-Bueno, Olivan-Palacios and Vgontzas) or developmental narcolepsy present other dilemmas to the caregiver. Often these children will also exhibit breathing difficulties while asleep, some as severe as sleep apnea. Children who display one of the many variants of nocturnal epilepsy present yet other problems as many of these may harm themselves during a seizure. Nocturnal frontal lobe epilepsy, though not discussed in the text under review, is particularly interesting given the seizure locus in the frontal lobes. In adults the frontal lobes are 'de-activated' or actively inhibited during REM sleep. Children with nocturnal frontal lobe epilepsy experience between 4-11 attacks per night with hyperkinetic thrashing and clonic jerking. More than two-thirds of the children remain aware during the attacks and experience fear, difficulty breathing and choking sensations. They frequently vocalize with a moan or a grunt or crying. The seizures typically occur in stage II non-REM and sleep fragmentation suggests intrusion of REM into NREM stages. Simakajornboon and Beckerman briefly cover developmental neuromuscular disorders in Chapter 17. As with a majority of the other developmental syndromes covered in this text, children with neuromuscular disorders are at higher risk for REM-related oxygen desaturation and hypoventilation. Virtually all these children evidence sleep-disordered breathing. Congenital myotonic dystrophy, though mentioned only briefly in this chapter, is an instructive disorder. Onset is in the neonatal period with hypotonia, poor grasping, suckling and swallowing responses, and multiple sleep-related respiratory problems. Even after the neonatal period these children have serious sleep disorders including hypersomnolence, excessive daytime sleepiness and sleep-onset REM periods (SOREMPs). The sleep problems persist even after correction of the pulmonary problems. It is as if the sleep system is not allowed to mature at a normal rate and so the neonatal pattern of hypersomnolence and SOREMPs are inappropriately retained. Similarly maturational delay of sleep system components is suggested in Autism, in this case REM (p. 185). The selective effect on REM in this syndrome produces a different array of symptoms than those seen in the neuromuscular disorders. In autism-spectrum disorders REM-related parasomnias are prominent. Dream recall may be reduced or absent in Asperger syndrome. In contrast to classical autism, Rett syndrome affects primarily females and neurologic impairments are progressive. The child is 'allowed' to develop some neurologic skills which are then progressively lost as the disorder develops. Sleep states are disturbed at every stage of the disorder with nighttime laughing, screaming and crying. Although reduced REM is common to many developmental disorders manifesting intellectual impairment Smith-Magenis syndrome (SMS, p. 88) may occassionaly be associated with a complete absence of REM. Children with SMS may also evidence prolonged nocturnal wakings.

How can a better understanding of genomic imprinting help us help these kids? Before discussing the book by Haig, let me first more accurately define genomic imprinting.

Genomic imprinting refers to the silencing of one allele of a gene according to its parental origin. The 'silencing' or tagging of the DNA probably involves methylation of CpG-rich domains. Thus, each cell in the progeny

recognizes and expresses only one allele of a gene locus, namely either the paternally-derived or the maternally-derived allele. The pattern specific monoallelic expression of imprinted genes results in a bias in the inheritance of traits with some traits inherited down the matriline and others down the patriline. Most of the genes identified to date as imprinted code for proteins that influence early growth with paternally imprinted or silenced genes tending to inhibit growth and maternally imprinted genes enhancing growth. In sum paternally expressed loci increases and maternally expressed loci restrains allocation of resources by the mother to offspring.

Imprinted genes, furthermore, directly impact development of brain systems. Keverne et al., (1996) presented convincing experimental evidence which shows that functionally distinct regions of the brain may reflect the distinct contributions of the maternal and paternal genomes. Keverne and colleagues examined embryological development in mice possessing only maternal (parthenogentic, PG) or paternal (androgenetic, AG) chromosomes. They produced a chimeric mouse containing a mixture of cells with either the single parent or normal complement of chromosomes (wildtype). When they compared AG to PG wildtypes they found that the distribution of PG and AG cells formed strikingly reciprocal patterns whereby PG cells were concentrated in cortical and striatal structures but excluded from hypothalamic, septal and pre-optic areas with AG cells showing the opposite pattern. These data show how imprinted genes impact brain development including development of specific brain regions that may be implicated in neurodevelopmental disorders of sleep. Developmental REM sleep, after all, appears to involve differential activation of hypothalamic and limbic systems, the brain systems that preferentially express AG cell lines (maternally imprinted/paternally expressed genes). It is becoming increasingly likely, therefore, that through their impact on brain development, systems of imprinted genes may also impact selected aspects of sleep development.

Now, Haig, predicted the fact that imprinted genes would typically code for proteins that influence early growth. He also predicted that paternal line genes would tend to enhance growth, while maternal lines genes would tend to moderate or restrict growth. These predictions have largely (though not always) been confirmed (Tycko and Morrison, 2002). The first 3 essays reprinted in the volume under review are the papers Haig wrote (beginning around 1988 right after the discovery of imprinted genes) which laid out the theory behind the predictions. It should be noted also that some of these papers included co-authors whom Haig gives full credit to for help in deriving his theoretical predictions.

To begin to understand the essays (some of them littered with rather forbidding mathematical analyses) reprinted in the volume under review we need to situate Haig's theoretical work in the longer tradition of evolutionary conflict theory. Organisms are composed of multiple genetic entities that do not always share the same genetic interests because they have different modes of inheritance. Different transmission patterns of genes to offspring create the context for conflict or negative fitness covariance between two associated or antagonistic genes. For example, genes that are normally passed on by only one sex, such as mitchondrial genes inherited through the female line, differ in their transmission patterns from Y chromosome genes inherited through the male line, and can therefore enter into conflict with them. If maternal line genes, for example, can increase their likelihood of transmission by decreasing transmission probabilities of paternal line genes then they will do so.

Evolutionary conflict can also occur among the autosomal genes of mother and offspring. Trivers (1974) pointed out that parent-offspring conflict likely influences a number of traits in mammalian life-histories. Parents and offspring

share only 50% of their genes. Thus there is plenty of room for conflict. Parental expenditure of time and resources on one offspring has an opportunity cost that means less time and resources are available for other (perhaps future) offspring. Offspring are predicted to attempt to acquire more parental investment and resources than parents are selected to supply. Parent-offspring conflict arises because genes expressed in offspring will evolve to discount benefits and costs to a parent's residual reproductive value relative to costs and benefits to the offspring's reproductive value.

Several of the essays reprinted in the volume summarize Haig's ongoing efforts at development of formal, game-theoretic models of imprinting effects in terms of the opposing effects of patriline and matriline genomes on growth and development. Haig conceptualized the evolution of genomic imprinting in terms of a process of genetic conflict between the maternal and paternal genomes that obtains whenever there is uncertainty about paternity of offspring (which is considered to be the case for human biology). Because a paternal gene in one offspring is unlikely to be in its siblings or its mother, the paternal gene can increase its chances of getting into the next generation (i.e. its fitness) if it promotes extraction of resources from the mother regardless of costs to the mother or its siblings who, in the context of paternity uncertainty, may carry genes of another male parent. The maternal gene, by contrast, is in all the siblings and thus its' fitness is increased by favoring cooperation and sharing of resources.

Thus, paternal line genes are more likely to foster aggressive prenatal and postnatal growth schedules while maternal line genes are more likely to modulate, restrain or inhibit aggressive rates of growth and development. Because these maternal and paternal genomes act antagonistically with respect to allocation of maternal resources and control of growth schedules, they also tend to promote internal brain and biobehavioral systems that function antagonistically around growth, reproductive behaviors and adult behavioral repertoires more generally.

Ongoing work in the molecular genetics of imprinting continues apace (to follow it see www.geneimprint.com) and thus there is a rapid accumulation of knowledge about imprinting effects on all sorts of neurodevelopmental phenomena. With Haig's theoretical formulations as a guide, along with the rapid accumulation of catalogs of imprinted genes and data on physiologic effects of these genes, it is time to look at ways in which imprinted genes may contribute to neurodevelopmental disorders of sleep. To conclude this book review I here summarize only a few potential avenues of research.

Two neurodevelopmental disorders of sleep that appear to be linked to imprinting anomalies (and are reviewed in the Wiggs and Stores volume) are Prader-Willi syndrome (PWS) and Angelmann syndrome (AS). Human chromosome area 15q11-13 is sometimes called the Prader-Willi/Angelman region because genes responsible for these disorders are located in this region. Angelman and Prader-Willi are neurodevelopmental syndromes that involve opposite contrasting sleep state changes. Prader-Willi syndrome is associated with maternal additions/paternal deletions of alleles at chromosome 15q11-13 and is characterized by poor sucking response, temperature control abnormalities and excessive sleepiness. Sleep architecture changes have also been noted in children and young adults with PWS, most specifically REM sleep abnormalities such as sleep onset REM periods or SOREMP, REM fragmentation, intrusion of REM into Stage 2 sleep and short latencies to REM (Hertz et al., 1993; Vela-Bueno et al., 1984; Vgontzas et al., 1996).

Conversely, Angelman syndrome is associated with paternal additions/ maternal deletions on chromosome 15q11-13 and is characterized by prolonged sucking, severe

mental retardation and reductions in sleep. These children may sleep as little as one to five hours a night with frequent and prolonged night wakings (Clayton-Smith & Laan, 2003; Zhdanova, Wurtman, & Wagstaff, 1999). One of the genes thought to be responsible for AS is UBE3A or ubiquitin-protein ligase E3A, which is expressed only from the maternal allele in certain brain tissues. These are the hippocampus and Purkinje cells of the cerebellum. This fact may be important for models of sleep and hippocampal memory function given that UBE3A is expressed biparentally in all other tissues.

Using recombinant and inbred strains of mice, Franken, Chollet & Tafti (2001), recently identified quantitative trait loci for a trait that modifies the rate at which need for slow wave sleep (SWS or delta power) accumulates. A QTL on mouse chromosome 2 homologous to human chromosome area 20q13.2 was identified. This region is known to be an imprinting control region. Franken et al. point out that several genes at or near this locus likely participate in SWS regulation. Franken et al. point out that the genes for growth hormone releasing hormone (GHRH) and the somatostatin receptor are also localized near 20q13.2. Along with growth hormone (GH), these hormones participate in regulation of both NREM and REM sleep processes. GH is released during NREM while somatostatin is released during REM. Varying levels of somatostatin exert varying effects on GH release. When SS reaches trough (but not zero) levels, pulsatile release of GH is facilitated while high levels of SS are associated with inhibition of GH release and NREM sleep.

There are a number of sleep disorders associated with genes encoded in the 20q13.2 region. Anokhin et al. (1992) identified a locus at 20q13.2 linked to so-called "low voltage EEG disorder" which involves a gradual loss of alpha waves in the EEG. Under normal physiologic conditions alpha waves gradually diminish as a person falls to sleep and descends into each successive stage of NREM. Another sleep-related disorder linked to a gene at 20q13.2-q13.3 is nocturnal frontal lobe epilepsy. As mentioned above the patients undergo seizures during the night whose focus is localized to the frontal lobes (Provini et al., 2000). Steinlein et al. (1994) suggested that the location of CHRNA4 in the 20q13.2 region made it a possible candidate gene for either benign neonatal familial convulsions (EBN1) or the electroencephalographic variant pattern 1 (EEGV1). Finally, Ondine's curse or central hypoventilation syndrome (which manifests during sleep), as well as congenital failure of central ANS control have been linked to markers at 20q13.2. Given REM's respiratory and ANS instabilities (see below) the link is interesting.

Another large imprinting domain in humans is at 11p15.5. The subtelomeric region of 11p (11p15.5) contains 3 genes IGF2, INS and TH (tyrosine hydroxylase) that lie in an interval of less than 50kb all of which have been implicated in sleep mechanisms, risk for cardiovascular traits and a neurodevelopmental disorder called Beckwith –Widemann syndrome (BWS). BWS is characterized by somatic overgrowth in the neonate and a predisposition to tumor in the early years. Twenty-five to 50% of patients with BWS have duplication of the active paternal copy of IGF2. Another 50% have an epigenetic mutation resulting in loss of imprinting of a transcript called KCNQ1OT1 (Weksberg et al., 2003). KCNQ1OT1 is a paternally expressed antisense transcript within KvLQt1 otherwise known as KCNQ1. KCNQ1 is a potassium channel gene involved in the long QT syndrome. It is maternally expressed in several tissues but not in the heart.

The serotonin 2a receptor (5HT2AR) at 13q14-q21 appears to be expressed from the maternal allele though polymorphic imprinting of the gene and may be the rule in adult human brain (Kato et al., 1996). Many of the new generation of anti-psychotics target this receptor and thus it may also be implicated in

pathogenesis of schizophrenia. Indeed, linkage and genetic association studies have pointed to polymorphisms in the gene as a contributing factor to schizophrenic symptomology (Dean, 2003). Antipsychotic agents antagonize the 5HT2A receptor thereby improving prefrontal cortical function and schizophrenic symptomology.

Several studies have directly linked the 5HT2A receptor to regulation of sleep mechanisms (Amici et al., 2004; Kirov & Moyanova, 1998; Landolt et al., 1999; Mayer, 2003; Monti & Monti, 1999), including regulation of REM.

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