Melatonin and Mental Capacities in Newborn Infants

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Objectives To investigate the role of melatonin in the emergence of mental capacities in the newborn infant.
Study design Assessment of Preterm Infant Behavior examination was performed at 2 weeks post-term age for 39 (21 preterm and 18 term) infants. 6-Suphatoxymelatonin from nocturnal urine samples was analyzed by enzyme-linked immunosorbent assays, and the Mental Developmental Index, assessed by Bayley scales, was correlated at 4, 6, and 9 months' corrected age.
Results Multivariate analysis of variance with repeated measures showed that improved autonomic function at 2 weeks of age was associated with higher Mental Developmental Index scores at 9 months when related to the amount of melatonin at 4, 6, and 9 months of age.
Conclusions Early compromised autonomic system function in preterm infants is associated with lower mental capacities and is related to lower melatonin levels at later ages. *(J Pediatr 2011;159:99-103)*.

When compared with term infants of comparable postmenstrual ages, medically low-risk preterm infants score on average 5 to 10 points lower on the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development.[1,2] Medically high-risk preterm infants demonstrate even greater deficits.[3-6] The lower MDI scores and the compromised attention control may be attributed to environmentally stressful conditions in the Neonatal Intensive Care Unit (NICU)[7] and differences in preterm infant brain development.[8] Suprachiasmatic nucleus (SCN) cells, the primary controllers of circadian rhythms, and SCN afferent and efferent pathways, emerge in fetal life and continue to develop after birth. The SCN can be identified in humans around mid-gestation and completes its development at 18 months post-term age, on average.[9] Fetal rhythms during pregnancy correspond to the external circadian rhythm due to the effect of the mother's hormonal activity and the environmental cycles to which she is exposed.[10] The newborn infant loses the coordinating signal, apparently produced by the mother. Blood and urine melatonin levels are not detected before 8 weeks after term.[11] Melatonin rhythmicity is established at about 8 to 12 weeks after a term delivery.[12] Higher vagal tone is associated with better mental function,[13] and higher oxygenation levels are associated with improved sleep patterns in preterm infants.[14] This suggests a link between the melatonin metabolism and the development of the autonomic system in preterm as compared with term infants. Reduced secretion of melatonin potentially causes suboptimal oxygenation of the frontal lobe, thus compromising the development of cognitive capacities of the newborn infant. Delayed melatonin production in preterm infants has been well documented.[11,15] Melatonin is considered a powerful and readily available antioxidant and a scavenger of free radicals.[16,17] In light of the sympathetic control of melatonin production, the antioxidant effect of melatonin and its recent clinical use for treatment of respiratory distress syndrome,[18,19] we asked if the development of melatonin production is a mediator of the autonomic system's impact on mental development.

Methods

The study was approved by the institutional review board. Because seasonal effects on melatonin production in early life have been reported,[20] the infants participating in the study were all winter-born (October to March) and the recruitment process was completed within 6 months. Study inclusion criteria were (1) healthy mothers with singleton and twin infants born at 38 to 42 weeks of gestation for term subjects or born at 28 to 34 weeks of gestation for the preterm sample; (2) Apgar scores equal or better than 7 at 1 and 5 minutes after birth; and (3) 10^{th} to 90^{th} percentile in weight, and head circumference according to Israeli growth curves. Study exclusion criteria included diagnosis of genetic anomalies, congenital heart malformations, gastrointestinal disturbances, and central nervous system abnormalities. Infants and their mothers who met study criteria were randomly selected from a successive list of preterm and term births at a large urban medical center in Israel and were recruited with informed consent between 2 to 9 days after delivery.

The singletons and twins and boys and girls were matched between preterm and term groups. In the 6-month recruitment period, 46 infants qualified for

APIB	Assessment of Preterm Infant Behavior
MANCOVA	Multivariate analysis of covariance
MDI	Mental Developmental Index
NICU	Neonatal Intensive Care Unit
SCN	Suprachiasmatic nucleus

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the study. Of these, two refused to participate. Thus, 44 infants (22 term and 22 preterm) infants and their mothers constituted the study sample. Five infants (two pairs of term twins and a singleton preterm infant) were later excluded because of spoiled urine samples. Additional sample characteristics are shown in Table I.

Power analysis indicated that a sample size of 30 mother-infant dyads would be sufficient to show a significant effect for melatonin levels with a power of 90% and 5% risk of type α error. This calculation was based on the effect size found in term and preterm infants' melatonin secretion levels.[15,21]

The examiners of the neurobehavioral assessment, melatonin assays, and Bayley scales were all blind to infant group status and other developmental data. Mothers were blind to the research question associating melatonin to the emerging mental capacities and were only aware of the research title "melatonin in the first year of life."

Procedures

The preterm-born infants were exposed to bright intensive care lighting for 24 hours (day and night) until discharge from the hospital and then to natural cyclical day-night lighting at home for the rest of the study period. The term-born infants were exposed to 24 hours of bright lighting for 2 days after birth until discharged from the hospital and then to natural cyclical day-night lighting at home for the rest of the study period. The participating NICU implemented dimming of light of all infants upon completion of this study.

Melatonin Measurement

The mothers were instructed to collect their infants' nighttime diapers containing urine from 7 p.m. to 7 a.m. (1900 to 0700) at the ages of 4, 6, and 9 months' corrected age.[20,21] The procedures of urine extraction from the diapers and the enzyme-linked immunosorbent assay for determining the amounts of the melatonin metabolite 6-sulfatoxymelatonin in the urine of young infants were as described previously.[20,21]

Neurobehavioral Assessment

The Assessment of Preterm Infant Behavior (APIB)[22] is a widely used, comprehensive newborn behavioral assessment with sensitivity to differentiate among subgroups of infants of varying gestational ages and degrees of risk status assessed at 2 weeks' corrected age.[23] The APIB appears to be sensitive to the increase in cortical gray and white matter as well as onset of myelination in the last trimester.[24,25] The assessment presents increasingly demanding environmental inputs in a graded sequence of distal and proximal stimulus presentations, which are based on the Neonatal Behavioral Assessment Scale.[26] The APIB six summary system variables were used in this

Table I. Demographic and medical background

Variable	Group	Mean/n	SD	T/χ^2	P
Gestational age at birth	Preterm	31	1	16.1	<.0001
	Term	38	1		
Apgar 1 min	Preterm	8	1	0.9	NS
	Term	8	1		
Apgar 5 min	Preterm	9	0.6	1.8	NS
	Term	10	0.3		
Birth weight	Preterm	1642	353	11.4	<.001
	Term	3073	424		
Birth weight percentile	Preterm	59	20	1.1	NS
	Term	51	20		
Head circumference at birth	Preterm	28	2	8.9	<.001
	Term	33	1		
Head circumference percentile at birth	Preterm	45	22	0.8	NS
	Term	51	19		
Maternal age	Preterm	33	7	1.2	NS
	Term	31	5		
Paternal age	Preterm	36	5	0.9	NS
	Term	34	6		
Paternal education	Preterm	13	2	1.4	NS
	Term	12	2		
Maternal education	Preterm	13	1	1.2	NS
	Term	14			
Mode of delivery (number of vaginal deliveries, number of cesarean section deliveries)	Preterm	9, 12		16.6	<.001
	Term	13, 7			
Mode of feeding (number of breast-fed infants, number of formula- and breast-fed infants, number of formula-only–fed infants	Preterm	0,9,12		28.4	<.03
	Term	13,2,3			
Surfactants (n)	Preterm	7		16.0	<.001
	Term	0			
Bronchodilators (n)	Preterm	8		13.5	<.001
	Term	0			
Respirator assistance (days range, 1-9) (n)	Preterm	8		13.5	<.001
	Term	0			
Intravenous feeding (n)	Preterm	19		35. 1	<.001
	Term	0			