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Decreased Arousals Among Healthy Infants After Short-Term Sleep Deprivation

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ABSTRACT. *Objective.* Sleep deprivation is a risk factor for sudden infant death syndrome (SIDS). Recent changes in normal life routines were more common among SIDS victims, compared with control infants. Sleep deprivation can result from handling conditions or from sleep fragmentation attributable to respiratory or digestive conditions, fever, or airway obstructions during sleep. Compared with matched control infants, future SIDS victims exhibited fewer complete arousals by the end of the night, when most SIDS cases occur. Arousal from sleep could be an important defense against potentially dangerous situations during sleep. Because the arousal thresholds of healthy infants were increased significantly under conditions known to favor SIDS, we evaluated the effects of a brief period of sleep deprivation on sleep and arousal characteristics of healthy infants.

Design. Fourteen healthy infants, with a median age of 8 weeks (range: 6–18 weeks), underwent polygraphic recording during a morning nap and an afternoon nap, in a sleep laboratory. The infants were sleep-deprived for 2 hours before being allowed to fall asleep. Sleep deprivation was achieved by keeping the infants awake, with playing, handling, and mild tactile or auditory stimulations, for as long as possible beyond their habitual bedtimes. To avoid any confounding effect attributable to differences in sleep tendencies throughout the day, sleep deprivation was induced before either the morning nap or the afternoon nap. Seven infants were sleep-deprived before the morning nap and 7 before the afternoon nap. The sleep and arousal characteristics of each infant were compared for the non-sleep-deprived condition (normal condition) and the sleep-deprived condition. During each nap, the infants were exposed, during rapid eye movement (REM) sleep, to white noise of increasing intensity, from 50 dB(A) to 100 dB(A), to determine their arousal thresholds. Arousal thresholds were defined on the basis of the lowest auditory stimuli needed to induce arousal. After the induced arousal, the infants were allowed to return to sleep to complete their naps.

Results. Sleep deprivation lasted a median of 120 minutes (range: 90–272 min). Most sleep characteristics were similar for the normal and sleep-deprived conditions, including sleep efficiency, time awake, percentages of REM sleep and non-REM sleep, frequency and duration of central apnea and of periodic breathing, du-

ration of obstructive apnea, mean heart rate and variability, and mean breathing rates during REM sleep and non-REM sleep. After sleep deprivation, the duration of the naps increased, whereas there were decreases in the latency of REM sleep and in the density of body movements. More-intense auditory stimuli were needed for arousal when the infants were sleep-deprived, compared with normal nap sleep. Sleep deprivation was associated with a significant increase in the frequency of obstructive sleep apnea episodes, especially during REM sleep. No significant differences were noted when the effects of morning and afternoon sleep deprivation were compared. No correlation was found between the duration of sleep deprivation and either the frequency of obstructive apnea or the changes in arousal thresholds, although the infants who were more sleep-deprived exhibited tendencies toward higher auditory arousal thresholds and shorter REM sleep latencies, compared with less sleep-deprived infants. There were tendencies for a negative correlation between the auditory arousal thresholds and REM sleep latencies and for a positive correlation between the auditory arousal thresholds and the frequencies of obstructive apnea during REM sleep.

Conclusions. Short-term sleep deprivation among infants is associated with the development of obstructive sleep apnea and significant increases in arousal thresholds. As already reported, sleep deprivation may induce effects on respiratory control mechanisms, leading to impairment of ventilatory and arousal responses to chemical stimulation and decreases in genioglossal electromyographic activity during REM sleep. These changes in respiratory control mechanisms could contribute to the development of obstructive apnea. The relationship between the development of obstructive apnea and increases in arousal thresholds remains to be evaluated. Adult subjects with obstructive sleep apnea exhibited both sleep fragmentation and increases in arousal thresholds. Conversely, sleep deprivation increased the frequency and severity of obstructive sleep apnea. In this study, the increases in arousal thresholds and the development of obstructive apnea seemed to result from the preceding sleep deprivation. The depressed arousals that follow sleep deprivation have been attributed to central mechanisms, rather than decreases in peripheral sensory organ function. Such mechanisms could include disturbances within the reticular formation of the brainstem, which integrates specific facilitatory inputs, such as ascending pathways from auditory receptors, and inhibitory inputs from the cortex. It remains to be determined whether the combination of upper airway obstruction and depressed arousability from sleep contributes to the increased risk of sudden death reported for sleep-deprived infants. *Pediatrics* 2004;114:e192–e197. URL: <http://www.pediatrics.org/cgi/content/full/114/2/e192>; *apnea*,

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ABBREVIATIONS. NREM, non-rapid eye movement; REM, rapid eye movement; SIDS, sudden infant death syndrome.

The sudden unexplained death of sleeping infants <1 year of age, ie, sudden infant death syndrome (SIDS), is the principal cause of postneonatal death in industrialized countries. The mechanisms responsible for SIDS are still largely unknown.

The incidence of SIDS is enhanced by sleep deprivation.¹ Recent changes in normal life routines were more common for infants with SIDS than for control infants.^{2,3} During the 24 hours before death, future SIDS victims slept significantly less than control infants.² Sleep deprivation can result from handling conditions, as well as sleep fragmentation attributable to respiratory or digestive infections,^{4,5} fever,⁶ or airway obstructions during sleep.^{7,8} Almost 70% of SIDS victims had experienced minor intestinal or respiratory infections during the 24 hours preceding death.⁴⁻⁶ Compared with control subjects, future SIDS victims exhibited symptoms reminiscent of daytime fatigue, such as decreased responsiveness and fatigue during feeding.⁹

Arousal from sleep could be an important defense mechanism against potentially dangerous situations during sleep.^{10,11} Such situations include severe obstructive apnea, esophageal reflux, cardiac rhythm abnormalities, and external suffocation. If the infant is unable to wake up and resume normal cardiorespiratory control, then the abnormal condition is not interrupted and the infant may die.¹¹

Repeated investigations among SIDS victims have provided evidence of subtle central nervous system abnormalities, especially in the brainstem.^{12,13} It is possible that such injuries could impair sleep-wake controls and arousal mechanisms.¹³ Compared with recordings for matched control infants, sleep recordings collected among infants who eventually died as a result of SIDS were characterized by fewer body movements⁸ and arousals by the end of the night,^{14,15} when most SIDS cases occur. Prenatal and postnatal factors associated with increased risks for SIDS, such as maternal smoking, prone sleep position, and high ambient temperatures, were shown to decrease the infant's arousability from sleep.¹⁶⁻¹⁸ These studies led some to propose that the arousal threshold in the sleep of SIDS infants is higher than normal and that such infants may fail to arouse when a life-threatening event occurs.^{10,11} Because healthy infants' arousal thresholds increased significantly under conditions known to favor SIDS,¹⁶⁻¹⁸ we postulated that, when healthy infants were sleep-deprived, their arousal thresholds in response to auditory stimuli would be increased.

METHODS

Patients

Fourteen healthy infants were successively selected, between September 2000 and March 2003, from a larger group of healthy

infants recruited for a prospective research program on sleep-related behavior. The infants were eligible for the study if they met the following criteria: they were born to nonsmoking parents who used no alcohol or drugs, with no family history of SIDS, they were ~8 weeks of age, they slept supine, they had regular sleep-wake schedules with morning and afternoon naps, and their parents would actively contribute to the study. Parents who agreed to participate were aware of the study methods. They took care to ensure regular sleep-wake schedules for their infants in the days preceding the study and to avoid any changes in the sleep routine the night before the test.¹⁹ The aims and methods of the study were approved by the university ethics committee and were explained to the parents, who gave their informed consent and who participated actively in the study.

Monitoring Procedures

Monitoring was conducted in a quiet room at an ambient temperature, ranging from 21°C to 24°C (69.8°F to 75.2°F). All patients slept supine, without restraints. The infants wore their own pajamas and were covered with a blanket. The clothing and bedding corresponded to 3° Tog insulation. The following were recorded simultaneously: 8 scalp electroencephalograms with central, temporal, and occipital leads; 2 electro-oculograms; a digastric electromyogram; and an electrocardiogram. Respiratory movements were measured with thoracic and abdominal strain gauges, and airflow was measured with oral and nasal thermistors. Oxygen saturation was recorded continuously with a transcutaneous sensor (Nellcor, Pleasanton, CA). An actigraph was placed on 1 arm, to measure body movements. The data were collected with computerized polygraph recorders (Morpheus System; Medatec, Brussels, Belgium).

Sleep Deprivation

The infants were admitted to the sleep laboratory at 9 AM. After preparation for the test, they were breastfed or given standard cow's milk formula by their mothers, in the volumes usually administered at home. After feeding, they either were allowed to fall asleep (afternoon sleep deprivation schedule) or were sleep-deprived for ~2 hours before being allowed to fall asleep (morning sleep deprivation schedule) (Fig 1). Sleep deprivation was achieved by keeping the infants awake with playing, handling, and mild tactile or auditory stimulations for as long as possible beyond their habitual bedtimes. To avoid any confounding effect attributable to differences in sleep tendencies throughout the day, sleep deprivation was induced before either the morning or afternoon nap. Seven infants were sleep-deprived before the morning nap and 7 before the afternoon nap. The sleep and arousal characteristics of each infant were compared for the non-sleep-deprived condition (normal condition) and the sleep-deprived condition. During their naps, the infants were exposed to auditory challenges, to determine their auditory arousal thresholds. After the induced arousal, the infants were allowed to return to sleep to complete their naps.

Auditory Stimulation

The infants were exposed to auditory challenges during each nap, to determine their auditory arousal thresholds. White noise of increasing intensity was presented for 3 seconds via a loudspeaker (SCR Electronics, Paris, France), at a distance of 3 cm from either ear.¹⁸ The level of the audiometer had been calibrated previously with a sonometer (Bruël & Kjaer model 2209; B & K Medical, Copenhagen, Denmark) at an equivalent distance.¹⁸ The perception of the intensity of a sound in the auditory system depends on the frequency of this sound. Physical decibels were converted to and expressed in physiologic decibels (A). The sound level was increased by 10 dB, ranging from 50 dB(A) to 100 dB(A). The time between presentations was 1 minute. A complete auditory challenge lasted a maximum of 6 minutes. A challenge was interrupted when the infant awakened, as defined by opening of the eyes and/or crying, or when a stimulation level of 100 dB(A) was reached. The auditory signal was automatically identified on the sleep recording. In both normal and sleep-deprived conditions, the infants were tested during rapid eye movement (REM) sleep, after a minimum of 5 minutes in the sleep stage. Auditory challenges were administered during REM sleep only. That stage of sleep was chosen because transient brain activations are more

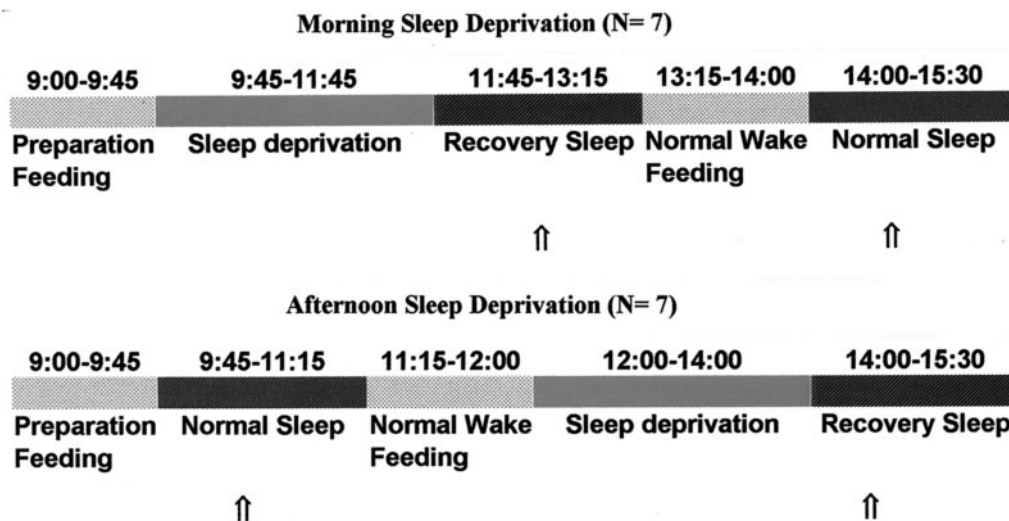


Fig 1. Study protocol. Auditory challenges (arrows) of increasing intensity, from 50 dB(A) to 100 dB(A), were administered during REM sleep in sleep-deprived and normal sleep periods.

readily seen in response to auditory stimulations during REM sleep, compared with non-REM (NREM) sleep.¹⁸ The challenges were not repeated in other sleep stages, to reduce the risk of sleep fragmentation and secondary increases in arousal thresholds.

Data Analysis

Sleep Stages

Each 30-second period of the sleep recordings was scored as NREM sleep, REM sleep, indeterminate sleep, wakefulness, or movement time, according to standard criteria.^{20,21} Before the auditory stimulations, sleep efficiency was defined as the time spent sleeping divided by the total recording time, multiplied by 100. The frequencies of NREM sleep, REM sleep, wakefulness, and movement were calculated by dividing the duration of each sleep state by the total duration of the period, multiplied by 100. Evaluation of the recordings was performed without knowledge of whether the infant was sleep-deprived or not.

Cardiorespiratory and Oxygen Saturation

Sleep apnea episodes were scored only if they lasted ≥ 3 seconds. Central apnea was scored when flat tracings were obtained simultaneously from the strain gauges and the thermistors. Periodic breathing was defined by ≥ 3 central apnea episodes separated by < 20 seconds of breathing movements. Obstructive apnea was scored when continuous deflections were obtained from the strain gauges while a flat tracing was recorded from the thermistors. Mixed apnea was defined as central apnea followed directly by obstructive apnea episodes and was scored together with obstructive apnea. Median values for oxygen saturation, heart rate, and respiratory rate were calculated for 1-minute stable sleep epochs. Overall heart rate variability was defined as the SD of the R-R interval values calculated between successive QRS complexes. Frequencies of apnea were calculated as an index by dividing the absolute number of events by the total sleep time of the period (in minutes) and then multiplying the result by 60.

Determination of Arousal Thresholds

An arousal was scored if, within 10 seconds after the start of an auditory stimulation, abrupt changes occurred for ≥ 3 seconds, including changes in body movements and increases in muscular tone and thoracic and abdominal respiratory signal amplitudes (with amplitudes at least twice as great as those measured before the stimulation), in association with an abrupt increase in electroencephalographic frequency.^{21,22} The breathing and electroencephalographic signals were compared with those recorded during the 20 seconds preceding the auditory challenge, to reduce the risk of spontaneously occurring arousals. Arousal thresholds were defined by the lowest auditory stimuli needed to induce arousal. Awakening was scored when the infant opened the eyes and/or cried.

Statistical Analyses

Statistical analyses were performed with the Wilcoxon matched-pairs test to compare the non-sleep-deprived condition and the sleep-deprived condition, with a level of significance of $P < .05$. The Spearman test was used for correlation studies.

RESULTS

The 14 infants studied included 4 male and 10 female subjects, with a median age of 8 weeks (range: 6–18 weeks). The median gestational age was 40 weeks (range: 36–41 weeks); the median birth weight was 3222 g (range: 2375–4515 g) and the median weight at the time of the study was 5355 g (range: 3900–6700 g). There was 1 premature infant, and there were 2 small-for-gestational age infants.

Sleep deprivation lasted a median of 120 minutes (range: 90–272 minutes). Most sleep characteristics were similar for the normal and sleep-deprived conditions. These characteristics included sleep efficiency (median: 94.6% in the sleep-deprived condition and 92.9% in the normal sleep condition; range: 66.4–100%), sleep latency (median: 0 minutes in the sleep-deprived condition and 5 minutes in the normal sleep condition; range: 1–152 minutes), time awake (median: 4.8% in the sleep-deprived condition and 6.3% in the normal sleep condition; range: 0–50.6%), REM sleep (median: 44.1% in the sleep-deprived condition and 37% in the normal sleep condition; range: 14.7–71.7%), and NREM sleep (median: 46.6% in the sleep-deprived condition and 41.5% in the normal sleep condition; range: 25.2–87.8%). No differences in the frequency and duration of central apnea, frequency of periodic breathing, median heart rate, heart rate variability, and breathing rate during REM sleep and NREM sleep were noted.

As shown in Table 1, the duration of the naps increased after sleep deprivation ($P = .003$), whereas there were decreases in the latency of REM sleep ($P = .003$) and in the density of body movements ($P = .041$). No significant differences were seen when the effects of morning and afternoon sleep deprivation were compared. More intense auditory stimuli were

TABLE 1. Differences Between the Two Study Conditions

	Sleep-Deprived Condition	Normal Sleep Condition	<i>P</i> Value
Sleep characteristics			
Nap duration, min	98.5 (42–165)	57.5 (46–78)	.003
Afternoon deprivation	101.5 (94–160)	59 (50–67)	.027
Morning deprivation	97.5 (42–165)	57.5 (46–78)	.046
REM sleep latency, min	10.5 (1–36)	20 (1–39)	.003
Body movements, %	8.18 (0–24.3)	14.15 (0–45.7)	.041
Breathing, obstructive apnea episodes (per h of sleep)			
Total sleep	0.90 (0–21.60)	0 (0–1.80)	.018
REM sleep	2 (0–29)	0 (0–4.2)	.008
Arousals from REM sleep			
No. of subjects with arousals	14/14	14/14	NS
Stimulus intensity, dB(A)			
Median (range)	70 (60–90)	50 (50–70)	.002
Mean \pm SD	72.3 \pm 13.6	54.6 \pm 7.7	

The values represent absolute values, median and range values, or mean and SD values. NS indicates not significant.

needed for arousal when the infants were sleep-deprived, compared with normal nap sleep ($P = .002$). Auditory arousal thresholds were not significantly different between morning deprivation [mean: 72.9 ± 13.6 SD dB(A)] and afternoon deprivation [mean: 71.7 ± 14.7 SD dB(A)] in the sleep-deprived condition; values were also similar in the normal sleep condition [mean: 54.3 ± 7.9 SD dB(A) for morning deprivation and 55.0 ± 8.4 SD dB(A) for afternoon deprivation]. No relationship was found between auditory arousal thresholds and gestational age, gender, birth weight, age or weight at the time of the study, or time or type of feeding. No difference in the frequency or duration of awakenings in the 2 study conditions was seen.

Sleep deprivation was associated with a significant increase in the frequency of obstructive sleep apnea, especially during REM sleep ($P = .008$). No difference was seen for the duration of obstructive apnea (median: 5.2 seconds in the sleep-deprived condition and 3.5 seconds in the normal condition; range: 3–9 seconds). After sleep deprivation, the frequency of obstructive apnea increased for 7 of 14 infants with respect to total sleep time and for 9 infants with respect to REM sleep. Some infants demonstrated greater increases in the frequency of obstructive apnea than did others. There was no correlation between the frequency of obstructive apnea and gestational age, age at the time of the study, birth weight, gender, or duration of sleep deprivation. If the 2 infants who experienced >15 obstructive apnea episodes/hour after sleep deprivation were excluded from the analysis, then the differences remained significant for the frequency of obstructive apnea during total sleep ($P = .043$) and REM sleep ($P = .018$), as for the arousal thresholds ($P = .005$).

Some infants could not stay awake during the 2 hours of sleep deprivation (3 infants in both the morning and afternoon deprivation groups), whereas some infants did not fall asleep at the end of the sleep deprivation period. Two infants in both groups fell asleep late, after 140 minutes and 172 minutes in the morning group and after 260 minutes and 272 minutes in the afternoon group. The infants who remained awake >120 minutes (median: 216 minutes; range: 140–272 minutes) did not differ ac-

cording to gender, gestational age, birth weight, age at the time of the study, type of feeding, or use of a pacifier from the infants who were less sleep-deprived (median: 90 minutes; range: 90–120 minutes). The infants who were more sleep-deprived exhibited a tendency to have higher auditory arousal thresholds [median: 75 dB(A); range: 60–90 dB(A)], compared with less sleep-deprived infants [median: 65 dB(A); range: 60–90 dB(A)]. After the nap, their auditory arousal thresholds were similar to those of the less sleep-deprived infants [median: 50 dB(A); range: 50–70 dB(A)]. They also exhibited shorter REM sleep latency (median: 6 minutes; range: 1–16 minutes), compared with less sleep-deprived infants (median: 11 minutes; range: 2–36 minutes), but they recovered to normal values after the nap (median: 19 minutes; range: 1–39 minutes). No significant differences in the frequency of obstructive apnea between the 2 groups of infants were observed. After exclusion of the more sleep-deprived infants, differences in arousal thresholds ($P = .012$), REM sleep latency ($P = .011$), and nap duration ($P = .017$) persisted, as did differences in the frequency of obstructive apnea during total sleep ($P = .042$) and REM sleep ($P = .018$).

No correlation was found between the duration of sleep deprivation and either the frequency of obstructive apnea or the changes in arousal thresholds. There was a tendency for a negative correlation between the auditory arousal thresholds and REM sleep latencies ($r = -0.36$, $P = .07$) and for a positive correlation between the auditory arousal thresholds and the frequency of obstructive apnea during REM sleep ($r = 0.34$, $P = .08$).

DISCUSSION

The infants' auditory arousal thresholds were significantly increased after a short period of sleep deprivation. The finding is reminiscent of reports of higher auditory arousal thresholds after sleep deprivation among human adult subjects.²³ One study of infants found no effect of short-term sleep deprivation on arousal propensity in response to visual or auditory stimuli.²⁴ The authors, however, did not evaluate the infants' arousal thresholds, as performed in this study.

The density of obstructive apnea episodes lasting ≥ 3 seconds was significantly increased after sleep deprivation. Sleep-deprived infants were reported to develop either nonsignificant²⁴ or significant²⁵ increases in the frequency of obstructive sleep apnea, according to the definitions of apnea duration. As reported for adults and animals, sleep deprivation might induce effects on respiratory control mechanisms, leading to impairment of ventilatory²⁶ and arousal²⁷ responses to chemical stimulation and decreases in genioglossal electromyographic activity during REM sleep.²⁸ These changes in respiratory control mechanisms could contribute to the development of obstructive apnea. The effects of sleep deprivation on respiration are related to postnatal maturation in lambs.²⁹ The development of obstructive apnea depends on a combination of anatomic, maturational, and environmental factors. The complexity of the mechanisms could be associated with the development of more frequent obstructions among some infants.

Our study has several limitations. First, the limited number of infants studied and the short duration of sleep deprivation could have prevented the finding of statistical significance for some of the changes observed after sleep deprivation. Second, we did not monitor the 24 hours at home before the test, to ensure that the sleep conditions were normal. We selected infants with regular sleep-wake schedules, including morning and afternoon naps. Because it was very difficult to recruit infants for this study, most of the challenged infants were children of doctors or nurses in our pediatric departments.¹⁹ Parents who agreed to participate were aware of the methods of the study and took care to avoid any changes in the infants' sleep routine before the test. Third, the studies were conducted in a laboratory environment, which might have disturbed the infants' sleep. Such effects would influence infants in both experimental conditions, however. Fourth, auditory challenges were administered during REM sleep only. That stage of sleep was chosen because transient brain activations in response to auditory stimulations are more readily observed during REM sleep than during NREM sleep.¹⁸ The challenges were not repeated in other sleep stages, to reduce the risk of sleep fragmentation and secondary increases in arousal thresholds. Additional studies are needed to determine whether these findings occur during NREM sleep.

The relationship between the development of obstructive apnea and increases in arousal thresholds remains to be evaluated. Adult subjects with obstructive sleep apnea exhibited both sleep fragmentation and increases in arousal thresholds.³⁰ Conversely, sleep deprivation increased the frequency and severity of obstructive sleep apnea.²⁵ In this study, sleep deprivation preceded the observation of an increase in arousal thresholds and the development of obstructive events. Both findings seemed to result from the preceding sleep deprivation.

Sleep characteristics change after sleep deprivation. Among adults, sleep deprivation induced an increased pressure to sleep, with a rebound in REM

and NREM sleep frequencies during the recovery night.³¹ Among infants, the total sleep time and the frequency of quiet sleep were increased during an undisturbed recovery sleep period after sleep deprivation.^{24,25} In this study, the duration of the nap significantly increased after sleep deprivation. The lack of significant changes in sleep structure could result from the short duration of sleep recorded before the administration of the auditory challenges.

The mechanisms responsible for the depressed arousals are not known. The depressed arousals that follow sleep deprivation have been attributed to central mechanisms, rather than decreases in peripheral sensory organ function.³² A functional dissociation between brainstem mechanisms and higher cortical and subcortical networks has been hypothesized.³² This could include a disturbance within the reticular formation of the brainstem, which integrates facilitatory inputs, such as ascending pathways from auditory receptors, and inhibitory inputs from the cortex.^{33,34} Intracortical motor inhibition induced by sleep deprivation could also contribute to the central mechanism.³⁵

CONCLUSIONS

Despite the limitations of our study, we showed that, after short-term sleep deprivation, healthy infants exhibited significant increases in both obstructive sleep apnea frequency and auditory arousal thresholds. It remains to be determined whether the combination of the development of upper airway obstruction and a depressed arousability from sleep contributes to the increased risk of becoming a victim of sudden death that has been reported for sleep-deprived infants.

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Decreased Arousals Among Healthy Infants After Short-Term Sleep Deprivation

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