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Review

Factors influencing the determination of arousal thresholds in infants – a review

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Abstract

Objective: To review the major confounding factors that influence the determination of arousal thresholds in infants.

Review of confounding factors: The determination of arousal thresholds in infants measures their arousability from sleep. The evaluation is influenced by various conditions. The infant's arousability is decreased by maternal factors, such as exposure to cigarette smoke, alcohol, illegal drugs or medications during gestation or breastfeeding. The levels of arousal thresholds also depend on the age of the infant and on experimental conditions, such as previous sleep deprivation, type of arousal challenges, time of administration of the arousal challenge, sleep stage, body position, room temperature, use of a pacifier, bed sharing, or type of feeding. In addition, spontaneous arousals can occur and modify the infant's response to external arousal challenges.

Conclusions: Factors known to modify infants' arousability from sleep should be controlled during studies designed to determine arousal thresholds.

Keywords: Sleep; Arousal; Non-rapid eye movement sleep; Rapid eye movement sleep; Arousal threshold; Environment

1. Introduction

Arousal thresholds are measured in infants to evaluate their arousability from sleep. An excessive propensity to arouse is found in infants suffering from insomnia and sleep disruptions [1,2]. A reduced arousability could lower the chance to survive in infants exposed to noxious conditions during sleep [3–9]. To determine arousal thresholds, sudden challenges are induced in the environment of the sleeping infant [10,11]. A variety of confounding factors influence the evaluation of the arousal thresholds, as will be reviewed in the present report [1,7,9,12].

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2. The determination of arousal thresholds

An arousal threshold is determined by measuring the intensity of the stimulus needed to arouse a sleeping infant. During the challenge, the subject's reactions are observed and continuous recording is done of electroencephalograph (EEG) and non-EEG parameters, such air flow, oxygen saturation, thoracic or abdominal movements. The scoring of the arousal reaction depends on the age of the subject. According to an American Sleep Disorders Association (ASDA) report, transient polygraphic arousals are defined by the occurrence over at least 3 s of an abrupt shift in electroencephalographic (EEG) frequency, associated (during rapid eye movement (REM) sleep) with an increase in electromyogram (EMG) submental ampli-

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Table 1
Factors that decrease the infant's arousability from sleep, seen as changes in spontaneous or induced arousals

	Effects	[Ref.]
Prenatal factors		
Drugs	Delayed arousal response to hypoxia	[19,22]
Cigarette smoking	Reduced arousal response to hypoxia	[18]
	Higher auditory threshold	[17]
Postnatal factors		
Increase in age	Decrease in spontaneous arousals	[14]
	Higher auditory arousal threshold	[21]
	Higher threshold to trigeminal stimulation	[12,25]
	Higher threshold to hypoxic arousal	[19,22]
	Higher threshold to vibrotactile arousal	[4]
Sleep deprivation	Decrease in spontaneous arousals	
Sedatives	Decrease in spontaneous arousals	[50]
Respiratory infections	Decrease response to pharyngeal water infusion	[47]
Experimental factors		
Time of the night	Changes in auditory threshold	[14,24]
Prone sleep position	Decrease in spontaneous arousals	[16]
	Higher auditory threshold	[35]
High room temperature	Higher auditory threshold	[38]

tude, or respiratory irregularity [13]. In infants under 12 months of age, a polygraphic arousal is scored when the infant appears asleep but simultaneously manifests abrupt EEG and non-EEG changes. EEG responses are seen principally in the occipital leads and include flattening of the EEG signals. In the young infant and the newborn, the well-known spontaneous variability in respiration, body movements and heart rate significantly complicates the evaluation of arousals. Autonomic and behavioral responses occur, such as abrupt changes in respiratory rate and amplitude, cardiac rhythm, muscle tone or galvanic skin values. Stereotyped reflexes can occur, such as a sigh followed by a startle. Incomplete awakenings are scored in the presence of incongruencies between EEG and other polygraphic parameters [14,15]. The scoring of arousal reactions in young infants thus largely relies on non-EEG changes.

2.1. Confounding factors in the determination of the arousal thresholds

Various confounding factors can interfere with the infant's arousal reaction. These include maternal, infant and experimental factors. Some factors increase, while others decrease the arousal thresholds (Tables 1 and 2). One should emphasize that many of the studies reported included only a limited number of subjects, and for many of them, have not yet been replicated.

2.2. Maternal factors

Some studies reported significantly higher arousal thresholds in newborns and infants prenatally exposed to nicotine and cigarette smoke. The finding was reported for newborns and infants of mothers who had smoked during gestation. When exposed to auditory [16,17] or hypoxic [18,19] arousal challenges, these newborns and infants had significantly higher arousal thresholds than subjects born to non-smoking mothers. The newborn's arousability is also depressed following maternal exposure to illegal drugs. Infants of substance-abusing mothers required a significantly longer exposure to hypercapnia before arousal than age-matched control infants [19]. A preliminary study reported that disturbances in spontaneous arousals occurred in neonates of mothers who consumed alcohol during the first trimester [20]. No data are yet available on the effects of alcohol consumption on the determination of arousal thresholds.

Table 2
Factors that increase the infant's arousability from sleep, seen as changes in spontaneous or induced arousals

	Effects	[Ref.]
Infant factors		
Pacifier	Increased spontaneous arousals	[51]
	Lower auditory arousal thresholds	[17]
Breastfeeding	Increased spontaneous arousals	[39]
	Lower auditory arousal threshold	[17]
Milk allergy	Increased spontaneous arousals	[52]
Prolonged apneas	Increased spontaneous arousals	[44]
Proximal esophageal reflux	Increased spontaneous arousals	[41]
Leg movements, pain	Increased spontaneous arousals	[13]
Experimental factors		
Bedsharing	Increased spontaneous arousals	[40]
Tracheobronchial stimuli	Increased spontaneous arousals	[46]
Increased blood pressure	Increased spontaneous arousals	[43]
Sleep stage		
Lower arousal threshold in active (REM) sleep from	Pharyngeal stimulation	[29]
	Auditory stimulation	[24,30]
	Vibrotactile stimulation	[4]
	Air jet to nostrils	[12,25]
	Light stimulation	[27]
	Airway occlusion	[31]
	Head-tilt challenges	[33]
Lower arousal threshold in Quiet (NREM) sleep from	Hypoxic/hypercapnic challenges	[19,22]

2.3. Infant's characteristics

Arousal thresholds depend on the age of the infant. Like spontaneous awakenings [14], arousal thresholds to auditory [21], trigeminal [12] or hypoxic stimuli [22] show an ontogenetic pattern, with a decrease in threshold level during the first 3 months of life. In one study, only 12.5% of infants older than 9 weeks aroused from NREM sleep when exposed to hypoxia compared to 70% of infants younger than 9 weeks of age [22]. As normal infants mature, their ability to arouse in response to hypoxia diminishes by 2–3 months of life. However, by the same age, an increase in vibrotactile stimuli arousal thresholds was reported [4]. The duration of the gestation can modify the infant's arousability. At 2–3 months of age, the arousal thresholds are greater in pre-term infants challenged by nasal air-jet stimulations during NREM sleep, than in infants born at term [23].

2.4. Experimental conditions that modify the infant's arousability

2.4.1. Sleep deprivation

Sleep deprivation increases arousal thresholds [24–27]. The effect is mainly seen during the second part of the night, for long-term losses of sleep. Following short-term sleep deprivation in infants, however, no detectable alteration was seen in arousal threshold to photic or auditory stimuli [27].

2.4.2. Type of arousal challenge

The type of challenge chosen to arouse the infant influences the level of the arousal threshold, as show in the following examples.

2.4.2.1. Hypoxic and/or hypercapnic challenges. Contrary to many arousal stimuli, arousal thresholds to hypoxia were lower in Quiet than in Active sleep [19]. In 18 healthy term infants younger than 7 months arousal thresholds to hypoxic challenges showed marked inter-individual variations in infants. Contrary to hypercapnia, hypoxemia is considered to be a poor arousal stimulus [19]. In real life conditions, hypoxemia is likely to be associated with a mild and transient increase in end tidal CO_2.

2.4.2.2. Auditory challenges. An unfamiliar auditory stimulus, such as a white noise or a pure tone was used in most experiments as meaningful or familiar sounds to modify the sleeper's arousal reaction [24]. No standard method exists for the administration of the auditory stimuli. In some studies, signal generator, speaker or headphone were placed equidistant to both ears. In other experiments, the sound generator was located closer to one of the infant's ears [15,21]. Some studies relied on several intensities of the stimuli administered both above and under the level of reaction to define supra- and infarliminar intensities of the challenge [10]. Other challenges were done with the administration of fixed levels of noises [18], while others used progressive increases in noises up to 100 or 120 dB [15]. The time between stimulations varied from a few milliseconds to 1 minute. The rapid repetition of the stimulus can favor the development of habituation and modify the sleeper's arousal responses. It was shown in 22 infants that rapid habituation of responses occur with repeated tactile stimulation to the foot, performed during daytime nap studies [28].

2.4.2.3. Time of the night. Infants responded poorly when exposed to auditory challenges during the first sleep cycle [12]. Arousal thresholds declined across the night, as a function of accumulated sleep time [21]. In infants born at term, arousal thresholds to pulsatile air jet applied to the nostrils increased progressively with time of Quiet sleep [23].

2.4.2.4. Sleep stages. Spontaneous awakenings occurred more frequently in infants sleeping in Active (REM) than in Quiet (NREM) sleep. Arousal thresholds to hypoxia were lower in Quiet than in Active sleep [22]. Arousal thresholds were lower in Active (REM) than in Quiet (NREM) sleep for diverse stimuli, such as pharyngeal [29], auditory [21,28,30], vibrotactile [4], pulsatile air jet to the nostrils [10], visual [24], airway occlusion [31,32], or head-up tilt challenges [33].

2.4.2.5. Body position during challenges. Body position during sleep significantly modified arousal responses in infants. Newborn and 3-month-old infants sleeping prone showed less arousals [16] and higher auditory arousal thresholds [33–36] than when lying supine. The effect of the prone sleep position was independent of the infant's usual sleep position and remained unexplained.

2.4.2.6. Room temperature. Newborns exposed to cold showed a decrease in sleep continuity and an increased frequency of active sleep and body movements [37]. Compared to what was observed during thermoneutrality, newborns sleeping in a warm environment had higher arousal thresholds to auditory stimuli, mainly by the end of the night.

2.4.2.7. Other environmental factors. Other factors known to favor spontaneous arousals in infants include the use of a pacifier [38], breastfeeding [39], or bedsharing [40]. Arousals thresholds occurred at significantly lower auditory levels in infants sleeping with a pacifier than in infants who do not use a pacifier [38], and in subjects breast-fed than in infants bottle-fed [39].

3. Internal arousal stimulations

Spontaneous arousals can occur while an infant is being exposed to arousal challenges. The experimenter may then find it difficult to score whether the infant responded to the challenge or woke up spontaneously, independently of the environment conditions. Various endogeneous stimuli were shown to induce arousals, such as esophageal reflux [41], leg movements, pain [11], and increases in blood pressure [42,43]. Prolonged apneas favored arousal in infants [44], while short apneas, both central and obstructive, were reported to be poor arousal stimuli [45]. In animal studies, pharyngeal fluid stimulation favored arousals from sleep [46], but the effects of laryngeal stimulations were impaired during respiratory syncytial virus infection [47]. The role of respiratory infections remains debated, as auditory arousal thresholds were found to be lower during Quiet sleep in young cats infected with feline herpesvirus, than in healthy kittens [48].

Obstructive sleep apneas induced in lambs favored arousals from both Quiet and Active sleep. The time to arousal was however longer in Active than in Quiet sleep, and was further increased with repetition of the upper airway obstructions [49].

4. Conclusions

The objective determination of infants' arousability from sleep contributes to our understanding of diverse clinical conditions, such as sleep discontinuities or some of the mechanisms responsible for the sudden infant death syndrome. There is however a need to control for confounding factors known to modify arousability from sleep when performing arousal challenges. Some of the major confounders have been reviewed. It is hoped that their presence or absence will be taken into account and described in reports on the evaluation of infants' arousability.

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