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Graded arousal responses in infants: advantages and disadvantages of a low threshold for arousal

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Abstract

Objective: To review studies of upper airway protective reflexes and other aspects of arousal from sleep.

Methods: Discussion of pertinant physiological studies.

Conclusions: Infant arousal from sleep incorporates two systems. The first comprises a group of periodically occurring reflexes serving cardiorespiratory homeostatic functions as well as providing for several aspects of normal growth and development. The second system is organized to respond to acute threats to survival during sleep. Both systems are integrated in a single arousal network originating in the brainstem. Full arousal occurs as a progression of events occurring sequentially and manifested by various innate motor and cardiovascular responses. During an arousal, rostral progression from brainstem to cortex is retarded by increasing inhibition which serves to decrease cortical arousals thereby preserving the integrity of rapid eye movement and non-rapid eye movement sleep states. Activation of brainstem arousal reflexes alone can cause recovery from obstruction sleep apnea episodes without the need for cortical arousal, a phenomenon more characteristic of infants than adults. © 2002 Published by Elsevier Science B.V.

Keywords: Sleep; Infantile apnea; Sudden infant death syndrome; Sleep startle; Augmented breaths

1. Introduction

There has been much interest in the physiological mechanisms causing arousal from sleep in the past 20 years when it became apparent that recovery from obstruction sleep apnea (OSA) episodes coincided with arousal related changes in the electroencephalogram (EEG) [1]. Further interest occurred when evidence suggested that sudden infant death syndrome (SIDS) might be caused by sleep apnea. Accordingly, it was proposed that difficultly in arousing from sleep could be causal in the pathogenesis of SIDS [2].

The present brief review focuses on research that initially was inspired by the need for better understanding of SIDS and infant apnea. Here, we discuss the neurophysiology of arousal with particular attention to the sequence of reflexive behaviors associated with arousal in infants. These and other observations suggest that arousal consists of two integrated functional systems, one necessary for homeostasis of cardiopulmonary function and the other for defensive response to danger. Discussion is focused on functional aspects of a 'graded' response to stimuli in which awakening is the final stage of sequential arousal.

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1.1. Neurophysiology of arousal from sleep

Much has been learned from studies in freely behaving animal models fitted with microelectrodes monitoring the brain activity leading up to arousals [3–5]. These studies show that arousal has its origin in the ascending reticular activating system of the brainstem. From there it spreads rostrally to the thalamus and finally to the cortex. This pathway is characteristic of both stimulus initiated and spontaneous arousals. The earliest activity in the brainstem is associated with changes in heart rate and blood pressure. These cardiovascular as well as altered respiratory patterns have served as physiologic markers for 'brainstem arousal'. Over the past 5 years, we have performed studies in sleeping human infants [6–11]. We have found additional motor behaviors indicating brainstem arousal. The earliest of these is an augmented breath or sigh having the distinctive configuration of a 'breath on top of a breath'. This can be associated with a sleep startle which occurs simultaneously with the second phase of the biphasic sigh. If the arousal process continues for 100–200 ms after onset of the startle, stereotyped whole body movements occur which we have termed 'thrashing movements'. This sequence of events can progress to cortical EEG activation and awakening with eye opening which then may progress to higher levels of arousal indicated by crying. These events generally occur in a fixed sequence with the earliest brainstem reflexive behaviors taking place prior to any indication of arousal in the thalamus. Importantly, the earliest events in the sequence occur more often than the later events. That is to say, isolated sighs are the most frequent occurrences. A sigh plus a startle is less frequent and this sequence followed by 'thrashing' is still less frequent. Progression to full arousal is the least frequent. From these observations, we conclude that the pathway to full arousal is regulated by increasing degrees of inhibitory influence in which most arousal activity, spontaneous or otherwise, is confined to the brainstem. In addition, behavior in the sequence is also 'graded' in that the magnitude of the behavior appears to influence the magnitude of following responses. Wulbrand and coworkers found that the amount of motor activity involved in startles predicts the duration of subsequent arousal related activity in the thalamus. The degree of thalamic activation was reflected in the duration of suppression of thalamic related spindle activity in the cortical EEG during non-rapid eye movement (NREM) sleep [10].

It is important to realize that in addition to spontaneous arousals, arousal producing stimuli of various types such as tactile, CO_2 increase or asphyxia produce the same sequential pattern of reflexes and EEG activity suggesting that a single common arousal pathway is utilized in all arousals [6,11]. Furthermore, arousals in rapid eye movement (REM) and NREM sleep have these same characteristics except for small differences in timing of the sequential responses.

1.2. Function of arousal related reflexes

Arousal in infants comprises both homeostatic and defensive functions. The respiratory and circulatory events during earliest arousal are integrated responses and are important in bodily homeostasis. It has long been appreciated that periodic augmented breaths are critical for maintaining lung compliance. Absence of sighs results in progressive atelectasis associated with pulmonary shunting and an increasing load on both the heart and respiratory muscles. The transiently increased heart rate and systemic vasoconstriction at onset of arousal may, in part, be secondary to increased venous return accompanying a sigh. These responses may also have a homeostatic function. Periodic change in body position caused by startle or 'thrashing' is important for maintaining skin perfusion of the dependent, weight-bearing surfaces. As well, such motor activity is important prenatally since periodic change in fetal limb position is necessary for normal limb development. Postnatally, changes in head position is required for symmetric head growth. These brainstem responses with effects on lung compliance and circulation also serve a dual protective function, particularly, in the young infant. In addition, startle and thrashing movements are important for airway protection. Infants sleeping prone and face down usually are in a potentially asphyxiating environment. As CO_2 rises and O_2 falls, head lifting movements during startle serve to clear the airway. If this does not improve access to fresh air, thrashing movements usually cause a repositioning of the head and face sufficient to clear the airway. In other situations, when an infant is sleeping and his head is covered by bedding, creating a potentially dangerous asphyxial environment, thrashing movements which usually include brushing hands to face activity may also clear the airway. But, usually airway clearance occurs only after the infant summons help by complete arousal with crying. Maturation of these stereotyped movements involves more purposeful and effective movements likely reflecting subcortical acquired responses. In a comparison study of sleeping adults in which the subject's head was covered by bedding during sleep, arousal onset occurred with an augmented breath as in infants [12]. However, unlike the stereotype infant responses, the adult movements were more directed and coordinated. These included grasping and tugging which caused cloth removal, usually prior to full arousal.

The rostral to caudal inhibition incorporated into the arousal responses would appear to serve two purposes. First it provides for periodic essential brainstem activities that do not interrupt sleep cycles. Uninterrupted cycles of REM and quiet sleep are essential for normal brain function during waking hours. It has become generally appreciated that individuals with frequent arousals caused by OSA episodes may suffer from decreased mentation when awake as well as daytime sleepiness and an associated increase in arousal threshold [13]. As well, interruption of REM sleep cycles in infants also appear to have delirious effects interfering with normal growth and development [14–17]. All in all, it appears that two cyclical processes, one needed for periodic motor activity and the other needed for complete arousal, utilize a single neural pathway that is regulated to prevent the frequent occurrence of complete arousal from sleep.

The apparent need for suppression of full arousal is further illustrated by habituation to stimuli that can cause arousal. McNamara and coworkers stimulated infants with periodic tactile stimuli during sleep [7]. They applied a quantified stimulus to the foot at frequent intervals. The initial response was foot withdrawal, which is a spinal reflex. This was followed by a sigh, startle, thrashing, and cortical arousal as indicated by EEG activity. With repeated stimuli, responses were eliminated starting with cortical activity, then startle followed by sighs and foot withdrawal until at last, single toe twitches were finally eliminated. There were some differences in REM and NREM sleep with more rapid habituation occurring in the former, however, the overall sequence was the same in both sleep states.

In the past, habituation has been viewed as a process where non-essential functions in response to insignificant stimuli are eliminated. During sleep, the least threatening stimuli such as a repeated noise can be eliminated and the sleep state cycles preserved. This does not preclude, of course, that minimal responses to stimuli are completely without function. Limb withdrawal along with startle likely serves a rudimentary protective function for sleeping infants such as thwarting attacks by insects or small predatory creatures. The set points for arousal thresholds are likely to be different for each individual. Thresholds may also be altered by other factors such as infection or sleep deprivation.

1.3. Apnea and SIDS

The concept of arousal being required for termination of apnea stems from observations on OSA in adults [1] and also from Sullivan and Phillipson's observations suggesting that cortical arousal was necessary for other defensive activities such as cough [18]. These considerations prompted the arousal theory for cause of SIDS along with early observations indicating that infants with apparent life threatening episodes had increased arousal thresholds as measured by full awakening to stimuli [2]. However, this SIDS theory needs to be modified in view of the more recent findings that complete arousal is not a prerequisite for recovery from OSA. Absence of cortical EEG change is the norm during recovery from OSA in infants [19,20]. Wulbrand and coworkers have provided a plausible explanation for the absence of EEG arousal in infants who spontaneously terminate obstructive episodes while sleeping [19]. At the termination of an obstructive episode, there are usually signs of some degree of arousal in the brainstem including one or more augmented breaths [19]. In experimental studies of airway occlusion in sleeping infants breathing through a face mask, Wulbrand and coworkers found that a sigh and startle always occurs after several seconds of airway occlusion [8]. Often, this was not associated with cortical arousal. They suggested that the increased airway maintaining muscle activity associated with a sigh combined with the airway dilating effect of neck extension could terminate the pharyngeal airway closure in OSA episodes.

It is further noteworthy that complete arousal may have little effect on terminating apnea and may actually provoke certain types of apnea and cardiac arrhythmia. Hence in prolonged apnea caused by stimulation of the laryngeal chemoreflex, Davies and co workers showed that behavioral arousal may occur during the episodes without any apparent effect on their duration [21]. Also, severe asphyxial episodes, termed infantile breathholding episodes or prolonged expiratory apnea, actually are associated with increased states of arousal and crying. Termination of these spells is associated with loss of consciousness due to extreme cerebral hypoxia [22]. Additionally, the often-fatal cardiac arrhythmia associated with prolonged QT syndrome in infants is frequently initiated by increased states of arousal.

1.4. Cultural manipulation of infant arousal from sleep

It is now well confirmed that frequency of arousals from sleep is decreased in infants sleeping prone as compared to those sleeping on their backs [23]. It is also been well established that prone sleeping infants are at greater risk for SIDS than back sleepers. This poses a problem for parents who rightfully perceive that their infants sleep better on their stomachs. Noting that their infant may go to sleep faster and sleep more soundly prone, they may opt for this sleep position.

Wrapping infants tightly in a blanket or sheet (swaddling) has been used for eons to promote sleep in infants [24]. Formerly, its use was nearly universal. In the last two centuries, swaddling has been abandoned by many western cultures, however, it is still in widespread usage around the world. Swaddled infants have been shown to have an increased threshold for arousal from various stimuli [25]. Recently, it has been shown by Gerard et al. that swaddling reduces incidence of spontaneous arousals in back sleeping infants [26]. Swaddling does not reduce frequency of augmented breaths but rather impairs the progression of the arousal sequence to startles and full arousal. Therefore, it appears to increase the inhibitory influence regulating the spreading of the arousal process from brainstem to cortex. How it does this is unclear but it could decrease proprioceptive stimuli for arousal originating in arms and legs associated with startles. A similar mechanism was suggested by Sherrington for propagation of 'chained' or allied reflexes in which the stimulus arising from one motor response serves as a stimulus for the next [27]. As previously noted, some have argued that decreased arousalibility may be a primary mechanism in which SIDS risk is increased in prone sleeping infants. If so, this would argue against swaddling supine infants. However, this argument is contradicted by findings from studies showing that swaddled infants have decreased risk for SIDS over and above unswaddled supine sleeping infants [28,29].

The interaction between sleep position and arousal threshold may depend on stimulus type. For example, arousal to asphyxia may have a different threshold than that to pure CO_2. Asphyxia is a complex stimulus, because hypoxia initially is stimulus for arousal but rapidly becomes a depressant. Hence the interaction of hypoxia and hypercapnea is not entirely predictable. This may explain why one research group recently noted that infants are less likely to arouse to CO_2 in the prone position compared to supine whereas others found that mild asphyxia produces just the reverse that is to say it more readily arouses prone sleeping infants compared to those sleeping supine [30,31].

1.5. Summary

In summary, the neural pathway for arousal from sleep incorporates two systems. The first being a group of periodically occurring reflexes required for pulmonary and cutaneous integrity as well as several aspects of normal growth. The second serves primarily in protection from threats to survival during sleep. Both are integrated in a single arousal network originating in the brainstem. Rostral progression from brainstem to cortex is retarded by increasing inhibition in such a way that decreases cortical arousals and preserves integrity of sleep states. Thus, a balance is maintained between too few and too many arousals. One advantage of this balance is that activation of brainstem arousal reflexes can cause recovery from OSA episodes in infants without the need for cortical arousal.

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