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EVOKED RESPONSES TO ELECTRICAL STIMULATION OF THE AUDITORY PATHWAY DURING THE WAKE/SLEEP CYCLE

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INTRODUCTION

Several studies have been reported on changes in auditory pathway responses during the wake/sleep cycle that are not in agreement. Many of the inconsistencies derived from failure to control for variations of stimulus input and for activity of middle ear muscles^{5,17}, both of which can effect large changes in auditory pathway responses independent of arousal, attention and sleep^{1,2,8,10,19}. Later studies which controlled these variables^{3,16} consistently report changes in auditory cortex and no change in cochlear nucleus evoked responses during the wake/sleep cycle, but conflicting data have been obtained for evoked responses at the inferior colliculus and medial geniculate.

In this study, we have investigated changes in auditory pathway during the wake/sleep cycle by recording responses evoked by electrical stimulation of brain stem and thalamic auditory nuclei. The electrical stimulus employed produced a clear evoked response similar to that obtained with clicks. The advantage of electrical stimulation of the auditory pathway is that it bypasses problems of acoustic input control and the effects of middle ear muscle activity. Moreover, electrical stimulation provides a means of tapping into different levels of the afferent pathway to define more precisely the locus of changes in transmission of auditory information.

MATERIAL AND METHODS

Ten adult cats were implanted with electrodes under barbiturate anesthesia. Subcortical sites were implanted with bipolar electrodes consisting of two 125 μ m stainless steel wires cemented to opposite sides of a steel tube (0.5 mm, outer diameter) and extending approximately 5 mm below the tube. They were insulated except at the tip and were cut at an angle to give approximately 0.5 mm separation in the verti-

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cal plane. Electrodes were placed stereotaxically in cochlear nucleus (5 cats), superior olive (2 cats), inferior colliculus (8 cats), medial geniculate (8 cats) and auditory radiations (2 cats) while monitoring evoked responses to clicks. Bipolar cortical electrodes consisting of two 250 μm stainless steel wires, separated by 1 mm in the vertical plane, were placed under visual control in A1 or Ep, as defined by Woolsey¹⁸. The lead electrode of the bipolar array penetrated approximately 1 mm into the cortex and the lag electrode rested on the surface of the cortex. Bipolar cortical electrodes were used in order to limit the cortical area from which responses would be recorded. Three screws with wires soldered to their heads were attached to the skull for EEG recording and ground. All electrodes were attached to the skull with dental cement, and then connected by crimping to a miniature head plug which was cemented to the skull. At least 10 days postoperative recovery was allowed before recording sessions were started.

During the experimental sessions, the animal was placed in a cage in a sound attenuating chamber where it could be observed through a one-way mirror. Two wound clips were placed in the skin over the neck for monitoring the EMG. The central nervous system bipolar electrodes could be used for either stimulation or for recording. A cable connected the plug on the cat's head to amplifiers (1.5–1000 c/sec) or to a constant current stimulator. The amplifier outputs were led into an 8-channel oscilloscope, a 2-channel penwriter for recording EEG and EMG, and to a small digital computer (Mnemotron CAT 400B). Electrical stimuli were unidirectional square wave pulses, 0.1 msec in duration, presented at a rate of 1/sec from an isolated constant current source. Stimulus strength was monitored by a current probe (Tektronix P6016) and displayed on an oscilloscope. The current intensities used varied from 100 to 700 μA depending on the particular electrode pair stimulated. We attempted to choose a value that elicited an evoked response when viewed on the oscilloscope but which produced no signs of behavioral arousal or stereotyped movement.

Each animal was used for several recording sessions lasting 4–6 h. In each session, one site was stimulated and evoked responses from higher sites were recorded. The average of 30 or 40 responses was obtained on the CAT computer and written out on an X–Y plotter. Stimulation was presented throughout the recording session, but data from the first 20 min of stimulation were discarded to avoid habituation effects. Habituation of the evoked response was regularly observed from the medial geniculate and cortical sites but not from inferior colliculus or superior olive. After the 20 min habituation period, recordings were made, and several averages were obtained during each session at each stage of the wake/sleep cycle. Amplitude measurements of responses were then made. The first 5 msec of the responses was usually discarded to eliminate shock artifacts. In responses whose latency was less than 5 msec (see Figs. 1 and 2) this was not necessary as shock artifacts were clearly visible at the beginning of the responses obtained.

Stages which were distinguished for the purpose of recording were as follows: (a) wake: sitting, head off ground, eyes open, desynchronized EEG; (b) slow wave sleep: lying down, head on ground, large amplitude slow wave EEG; (c) rapid eye

movement (REM) sleep: lying down, head on ground, desynchronized EEG, flat EMG. Eye movements were not recorded and no attempt was made to distinguish phasic changes associated with rapid eye movements from tonic effects characteristic of desynchronized sleep. Data were not analyzed from periods of drowsiness in which the EEG was characterized by spindles. Recordings were discarded if the animal was observed to make head or body movements during the averaging time. Records were not discarded, however, if the animal twitched during REM sleep.

After completion of data collection, animals were sacrificed, cortical electrode sites were noted visually and subcortical electrode locations were determined by examining histological preparations.

RESULTS

Superior olive, inferior colliculus

The records obtained from inferior colliculus (2 cats) and from superior olive (1 cat) of responses evoked by stimulation of cochlear nucleus showed no change in amplitudes through the wake/sleep cycle (Fig. 1).

Medial geniculate

The effect of the wake/sleep cycle on the responses evoked in medial geniculate varied as a function of the stimulating site. In one cat, the evoked response from cochlear nucleus stimulation was recorded and a clear change in response was seen (Fig. 2A). The response in slow wave sleep shows simplification of form and increased amplitude of the late slow wave. There is also a change in the response in REM compared with wakefulness. Although these changes between stages of sleep were consistent, responses showed some variability with each stage. Therefore, the ampli-

Fig. 1. Summed responses evoked by stimulation of cochlear nucleus during wakefulness (W), slow wave sleep (SS) and REM sleep. A, Sum of 30 responses recorded in superior olive (cat LM). B, Sum of 40 responses recorded in inferior colliculus (cat G). Inserts show location of recording electrodes. Responses in A were recorded from electrode location 1, responses in B from electrode location 2.

Fig. 2. Sum of 40 responses recorded in medial geniculate during wakefulness (W), slow wave sleep (SS) and REM sleep. A, Responses evoked by stimulation of cochlear nucleus (cat G). B, Responses evoked by stimulation of inferior colliculus (cat P). Insert shows location of electrodes from which responses A and B were recorded. Numerals refer to components of the responses which were measured and analyzed in Tables I and II.

tude of each component was measured, a Mann-Whitney U test was carried out comparing slow wave sleep and REM to wake responses, and mean percent changes in amplitude were calculated. These data are shown in Table I.

In contrast, the response evoked in medial geniculate from inferior colliculus stimulation (5 cats) showed no change as a function of the wake/sleep cycle. Re-

TABLE I

MEAN % CHANGE IN AMPLITUDE, IN SLOW WAVE SLEEP AND RAPID EYE MOVEMENT SLEEP COMPARED WITH WAKEFULNESS, OF 4 COMPONENTS OF RESPONSE SHOWN IN FIG. 2A

Mann-Whitney U Test: ** $P < 0.01$; * $P < 0.05$.

Component	SS				REM			
	1	2	3	4	1	2	3	4
P	-74.6 **	-46.5 *	-71.8 **	+82.6 **	+1.8	-62.0 **	+29.9 *	+7.4

TABLE II

MEAN % CHANGE IN AMPLITUDE, IN SLOW WAVE SLEEP AND RAPID EYE MOVEMENT SLEEP COMPARED WITH WAKEFULNESS, OF 2 COMPONENTS OF RESPONSE EVOKED IN MEDIAL GENICULATE BY STIMULATION OF INFERIOR COLLICULUS

Mean of data from 5 cats.

Component	SS		REM	
	Mean	Range	Mean	Range
1	-3.5	+8.1 to -12.7	-1.2	-25.0 to + 8.1
2	-1.7	+12.6 to -21.4	+1.1	+12.6 to +18.0

Fig. 3. Responses recorded in auditory radiations. A, Sum of 30 responses evoked by stimulation of superior olive (cat LM). B, Sum of 40 responses evoked by stimulation of inferior colliculus (cat G). Numerals refer to components measured and analyzed in Table III.

sponses from one of the animals is shown in Fig. 2B. The response morphology is relatively simple and some of the earlier components may have been masked by shock artifact. However, the two components of the responses which were measured showed no change (Table II).

Auditory radiations

The effect of the wake/sleep cycle on auditory radiation responses varied as a function of the stimulating site in a manner similar to data from medial geniculate (Fig. 3). In one cat in which superior olive was the stimulating site, responses in REM did not differ from wake, but were significantly smaller in slow wave sleep. However, with inferior colliculus stimulation, no changes were observed in responses in auditory radiations (Table III).

Cortex

Electrodes were placed in various locations in A1 and Ep as shown in Fig. 4. The types of changes in response during the wake/sleep cycle were characteristic of the

TABLE III

MEAN % CHANGE IN AMPLITUDE, IN SLOW WAVE SLEEP AND RAPID EYE MOVEMENT SLEEP COMPARED WITH WAKEFULNESS, OF 3 COMPONENTS SHOWN IN FIG. 3 OF RESPONSE EVOKED IN AUDITORY RADIATIONS

A, Response shown in Fig. 3A evoked by stimulation of superior olive. B, Response shown in Fig. 3B evoked by stimulation of inferior colliculus. Mann-Whitney U Test: ** $P < 0.01$; * $P < 0.05$.

Component	SS			REM		
	1	2	3	1	2	3
A	-65.2	-69.4	-31.1	-21.0	- 5.1	-3.8
P	**	**	*			
B	-24.0	-18.1	-21.3	-13.0	-12.4	+7.6
P

Fig. 4. Location of electrodes from which cortical evoked responses were recorded. ssa, anterior suprasylvian sulcus; eca, anterior ectosylvian sulcus; pps, pseudosylvian sulcus; ecp, posterior ectosylvian sulcus; ssp, posterior suprasylvian sulcus.

Fig. 5. Sum of 40 responses recorded in auditory cortex. A, Responses evoked by stimulation of medial geniculate recorded from electrode 2 (cat P). B, Responses evoked by stimulation of medial geniculate recorded from electrode 5 (cat P). C, Responses evoked by stimulation of inferior colliculus recorded from electrode 15 (cat O). Location of electrodes is shown in Fig. 4.

cortical location and were not dependent on locus of the stimulating electrode. For the purpose of the analysis, the response was divided into an early, short biphasic component (peak latency 8–10 msec) and a longer latency slow wave (peak latency 20–40 msec). Responses recorded from electrodes placed in A1, just anterior to the posterior ectosylvian sulcus, showed changes similar to those reported by other investigators: a simplification of early components of the response and an increased amplitude of the late slow wave in slow wave sleep (Fig. 5B). In responses recorded from electrodes in Ep (Fig. 5A) and in the anterior part of A1 (Fig. 5C), responses were large in REM and wake but were much reduced in amplitude or non-existent during slow wave sleep. In all sites there was no consistent difference between responses

TABLE IV

MEAN % CHANGE IN AMPLITUDE OF LATE SLOW WAVE, IN SLOW WAVE SLEEP AND RAPID EYE MOVEMENT SLEEP COMPARED WITH WAKEFULNESS, FOR EACH ELECTRODE SITE SHOWN IN FIG. 4

Data from all stimulating sites are combined in calculating mean values.

<i>Cortical region</i>	<i>Electrode</i>	<i>SS</i>	<i>REM</i>
Ep	1	—62.4	+10.1
	2	—90.5	+ 4.2
	3	—70.8	— 8.1
Posterior A1	4	+28.3	+ 5.6
	5	+89.9	—11.7
	6	+84.1	+ 4.2
	7	+65.2	— 6.1
	8	+31.5	— 8.2
	9	+71.3	— 3.1
	10	—21.0	+ 6.4
Anterior A1	11	—10.4	+12.2
	12	+32.6	+ 5.9
	13	+33.0	— 4.6
	14	—24.7	— 9.2
	15	—46.1	+ 3.1
	16	—11.3	— 6.4
	17	—31.0	+15.7
	18	—27.9	+ 7.6
	19	—18.1	— 9.1

recorded during wakefulness and during REM. Table IV shows mean percent changes in amplitude of the late slow component for each cortical electrode.

The early component of the evoked response was affected in a slightly different manner during the wake/sleep cycle. Electrodes 1–10, 12 and 17 showed a simplification of the early components of the response in slow wave sleep on 90% or more of the averages obtained. Electrode 16 showed loss of these components in slow wave sleep on only 50% of the averages, and electrodes 11, 13–15, 18 and 19 did not show an early response component in any stage of the wake/sleep cycle.

DISCUSSION

This study indicates that transmission at different levels of the auditory pathway is not affected in an uniform manner during the wake/sleep cycle. The amplitude of evoked responses in medial geniculate and auditory cortex to electrical stimulation of cochlear nucleus varies as a function of the wake/sleep cycle whereas responses recorded from inferior colliculus and superior olive are invariant. These results are in agreement with a variety of studies^{14,16,19} showing the transmission of information along the brain stem portion of auditory pathway is much more stable than transmission through the geniculate-cortical projections. The major sources of variability affecting brain stem responses are middle ear muscle activity and alterations in the

intensity of the acoustic signal reaching the ear. Both of these sources of input variability were effectively bypassed by the electrical stimulus employed in the present studies.

The observation of Berlucchi *et al.*³ that a late slow wave of the inferior colliculus response to clicks (latency around 100 msec) is modified during the wake/sleep cycle could not be confirmed both in the present study and in the one by Wickelgren¹⁶. Buser *et al.*⁴ have suggested that this late wave can be recorded from the lateral ventral part of inferior colliculus and that it represents corticofugal activity. In our animals all electrodes were placed dorsomedially or dorsolaterally and it is possible that the location of the electrode may be critical for detecting this late component.

The effect of the wake/sleep cycle on medial geniculate responses depended on the stimulus site. Stimulation of cochlear nucleus resulted in changes in medial geniculate responses similar to those reported by Wickelgren¹⁶ who used clicks. In contrast, medial geniculate responses evoked by inferior colliculus stimulation were unaffected by sleep/wake cycles. We are unable to resolve this paradox.

The inability of Berlucchi *et al.*³ to obtain changes in medial geniculate evoked responses to clicks during sleep may be technical in nature as they reported difficulty in obtaining good records from medial geniculate sites and they did not use averaging techniques.

A major finding in the present study is that cortical evoked responses showed clear and consistent changes during the wake/sleep cycle that depended upon the position of the electrode in auditory cortex. Electrodes located in the posterior region of A1 show the changes reported by other investigators (an enhancement of amplitude during slow wave sleep compared to wakefulness) whereas electrodes located at Ep and anterior A1 sites were affected in the opposite direction (an attenuation of amplitude during slow wave sleep compared to wakefulness). The difference between Ep and A1 changes during the wake/sleep cycle may be a function of different subcortical afferents to these two areas or may reflect changes in cortico-cortical transmission during the wake/sleep cycle¹³.

One other study involving central stimulation of the auditory pathways during the wake/sleep cycle has been reported⁶ and the authors postulate facilitation of transmission in medial geniculate during arousal and REM sleep to account for their results. They stimulated the brachium of inferior colliculus and recorded evoked response in radiations and cortex. They reported that in both sites the smallest evoked response was obtained in slow wave sleep, the largest in REM sleep. On stimulating radiations, however, they obtained a small evoked response in the cortex during arousal and a large evoked response in slow wave sleep and REM sleep. Their data on cortical responses are in conflict with ours and with those of other investigators summarized above. We did not observe consistent changes in radiation evoked responses from inferior colliculus stimulation, and we were not able to obtain clear cortical evoked response from stimulation of radiations. We cannot explain this discrepancy.

It is known the Ep responses are much more sensitive to barbiturates than A1 responses⁹ and midbrain reticular stimulation has been reported to facilitate Ep click

evoked response concurrently with no change in A1 responses¹⁵. These findings, and our data, suggest that the responsivity of sub-areas of auditory cortex is differentially affected by changes in level of arousal.

There is evidence for the visual and somatic sensory systems of tonic facilitation in thalamic transmission during REM. Pompeiano¹² notes this parallel in the visual and somatic systems, but concludes that in the auditory system changes at cortex appear to be of more significance than changes at medial geniculate. Our data support his conclusions that in the auditory system the cortex is primarily affected during the wake/sleep cycle. However, we did not find the consistent differences between responses recorded during wake and REM that other investigators have reported^{12,16}. There is some evidence, in the visual system, that the use of flashes and of electrical stimulation may give conflicting results^{7,11} and this may also prove true for the auditory system. No studies have been reported in other sensory systems investigating differential changes in sub-areas of primary receiving cortex during the wake/sleep cycle. If, as our data suggest, there is a change in the cortico-cortical transmission during the wake/sleep cycle, then a study of changes in responses in the different primary sensory cortices would be of interest.

SUMMARY

Cats with chronically implanted electrodes were used to study changes in the auditory pathway during the wake/sleep cycle. Evoked responses to electrical stimulation of brain stem and thalamic nuclei were recorded and the animals' state of arousal was determined by observation and by monitoring EEG and EMG. Evoked responses in superior olive and inferior colliculus were invariant during the wake/sleep cycle. Evoked responses in medial geniculate and auditory radiations showed significant changes in slow wave sleep compared with wakefulness when stimulated from nuclei below inferior colliculus. However, with inferior colliculus stimulation, no significant changes in response at medial geniculate or radiations were observed. Evoked responses recorded from posterior A1 cortical sites showed increased amplitude of the late wave and simplification of the early biphasic waves during slow wave sleep. In contrast, evoked responses recorded from Ep and anterior A1 sites decreased in amplitude or were absent during slow wave sleep compared to responses recorded during wakefulness. No significant differences between evoked responses recorded at cortex during wake or REM sleep were obtained. It is suggested that in the auditory system, the major changes occurring during the wake/sleep cycle are cortical in origin, and sub-areas of auditory cortex change differentially. Some change is also observed in medial geniculate only if stimulation is below the level of inferior colliculus.

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