CIRCADIAN AND ULTRADIAN RHYTHMS MODULATING THE SENSORY PROCESSING

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SUMMARY

The present review analyzes sensory processing during sleep and wakefulness from a single neuronal viewpoint. Our premises are that processing changes throughout the sleep-wakefulness cycle may be at least partially evidenced in single neurons by **(a)** changes in the discharge rate and firing pattern of the response to sound, **(b)** changes in the phase locking of the response to the hippocampal theta rhythm, and **(c)** changes in the effects of the neurotransmitters involved in the afferent and efferent pathways.

1. The concept that the neural network organization during sleep versus wakefulness is different and can be modulated by sensory signals and *vice versa*, and that the sensory input may be influenced by the CNS state, i.e., asleep or awake, is introduced. During sleep the evoked firing of auditory units increases, decreases, or remains similar to that

observed during quiet wakefulness. However, there has been no auditory unit yet that stops firing as the guinea pig enters sleep. Approximately half of the cortical neurons studied did not change firing rate when passing into sleep while others increased or decreased. Thus, the system is continuously aware of the environment. We postulate that those neurons that changed their evoked firing during sleep are also related to still unknown sleep processes.

2. The first part of our report is based on the hypothesis that the encoding of sensory information needs a timer in order to be processed and stored, and that the hippocampal theta rhythm could contribute to the temporal organization. We have demonstrated that the guinea pig auditory and visual neuronal discharge exhibits a temporal relationship (phase-locking) to the hippocampal theta waves during wakefulness and sleep phases.

3. Excitatory amino acid neurotransmitters participate in the synaptic transmission of the afferent and efferent pathways in the auditory system. In the inferior colliculus, however, the effects of glutamate mediating the response to sound and the efferent excitation evoked by cortical stimulation failed to show differences in sleep and wakefulness.

4. Considering that neonates and also infants spend most of the time asleep, the continuous arrival of sensory information to the brain during both sleep phases may serve to "sculpt" the brain by activity-dependent mechanisms of neural development, as has been postulated for wakefulness.

INTRODUCTION

Sensory information about the environment and the body continuously modulates central nervous system (CNS) activity during the sleep/wakefulness cycle. It has been postulated that wakefulness (W) was supported by the sensory systems and that a lack, or decreased level, in their activity would lead to sleep. In addition it has been reported interactions between sleep and sensory input in general, and a surgical *quasi*-total deafferentation revealed significant changes in the characteristics of sleep and wakefulness.

Although profoundly modified, the processing of sensory information is still present during sleep. While all sensory systems show some influence on sleep, they are also reciprocally modulated by the sleep or waking state of the brain. Moreover, every sensory system presents an efferent pathway with centrifugal fibers reaching its own receptors and nuclei of the afferent pathway. Thus, the incoming sensory information may alter sleep and waking physiology, and, conversely, the sleeping brain imposes rules on information processing.

Although we do not yet completely understand how the brain processes sensory information, it is currently accepted that neuronal networks can change depending on the information they receive throughout life. We postulate that neural networks can also change during the 24-hour cycling from wakefulness to sleep and *vice versa*.

THE SLEEP-WAKEFULNESS CYCLE: A CIRCADIAN RHYTHM

Sleep is a distinct physiological state in which the brain and the body in general show major changes of most physiological parameters compared to wakefulness. General phenomena such as brain metabolism and blood flow, brain oxygen availability distribution, energy metabolism, autonomic functions, temperature control and the endocrine system, illustrate how striking sleep-related changes, widely influence brain and body functions.

The electroencephalogram (EEG), together with other bioelectrical activities, such as the electromyogram, eye movements, and the hippocampal electrogram must be recorded to unambiguously differentiate between sleep and W, both in animals and humans. Briefly, in humans sleep stage 1 is characterized by a modified alpha rhythm and low amplitude EEG; stage 2 shows the typical spindles (14 c/s) and stages 3 and 4, which together constitute slow wave sleep (SWS), show an increasing amount of slow waves (3-4 c/s). Approximately 75% of one night's sleep is spent in stage 1, 2 and SWS. The remaining 25% of a single night's sleep in humans corresponds to paradoxical sleep (PS). This sleep phase is characterized mainly by EEG low amplitude-fast activity, rapid eye movements hypotonia/atonia of muscles with muscle twitches.

As stated by Moruzzi (1972), *"There is true sleep i) when the typical behavioral manifestations are present, ii) when arousal may be obtained with sensory or cortical stimulations and, finally, iii) whenever there is the typical alternation of synchronized and desynchronized phases"*.

The guinea pig sleep/waking cycle- not a circadian one- has been described as either diurnal or nocturnal. Although guinea pig's sleep is composed of SWS and PS stages, it occurs throughout the 24-hour period with a light/dark ratio of 1-1.1. This particular non-circadian condition is quite similar to the human neonate sleep-waking cycle.

AN EXPERIMENTAL APPROACH TO THE AUDITORY SYSTEM

Several reasons support our approach of relating sleep to auditory physiology. First, hearing is a tele-receptive modality relatively open during sleep, acting as a continuous monitor of the environment, e.g., predators detection, a baby´s cry during the night that awakes his parents. Second, while auditory stimuli can affect sleep, e.g., a noisy night will reduce the total sleep time and will be followed by a sleep normalization once the noise is reduced, the total lack of auditory input after bilateral lesion of the cochleae alters the sleep architecture of guinea pigs and hamsters by increasing the total sleep time. Third, the link between auditory perception and sleep is also expressed by the presence of auditory images in 65% of recalled dreams. Finally, the local blood flow is significantly increased in auditory *loci*, such as the auditory cortex, medial geniculate, inferior colliculus, superior olive, and particularly, the cochlear nucleus, with a ≈170% increase during paradoxical sleep.

THE HIPPOCAMPAL THETA RHYTHM: AN ULTRADIAN RHYTHM

The hippocampal theta rhythm is a well known feature of the hippocampal electrogram in humans and other mammals, although its principle function is unknown. Nevertheless, the hippocampus is involved in temporal and spatial positioning both associated with sensory input. Since the pioneering work of Scoville and Milner (1957), almost five decades of research resulted in the recognition that the hippocampus is involved in learning and memory processes in animals as well as in humans. It has also been related to muscular twitches during sleep and ponto-geniculo-occipital spikes as phasic PS phenomena, and with motor function.

The theta wave may affect spatially distant neurons by inducing fluctuations in cellular excitability due to membrane potential oscillations. Although more prominent in active W and PS, the hippocampal theta can also be observed during SWS.

Finally, the changes in neuronal firing in the auditory cortex evoked by electrical stimulation of the hippocampus represent evidence of a functional relationship between both regions of the brain.

In previous papers, our group has postulated that the hippocampal theta could play a role as an internal clock adding a temporal dimension to the auditory processing at the inferior colliculus and primary auditory cortex, to the visual processing in the thalamus and in the autonomic control of the heart rate, at least during PS, period in which the homeostatic controls decrease.

METHODS AND RESULTS

We used extracellular recording during the physiological sleep-waking cycle in restrained guinea pigs to study: 1. the firing rate and firing pattern of auditory neurons through the sleep-waking cycle; 2. the phase locking of auditory and visual neurons to the hippocampal theta rhythm; 3. neurotransmitter iontophoresis and receptor blocking of inferior colliculus neurons in sleep, waking and during electrical stimulation of the efferent system at the auditory cortex.

Auditory neurons firing in relation to sleep and wakefulness

The evoked and spontaneous unitary firing of the cochlear nucleus, the lateral superior olive, the inferior colliculus and the auditory cortex exhibited changes closely related to sleep and wakefulness stages. These changes were characterized by a firing increase or decrease and were associated, sometimes, with differences in the pattern of discharge. Changes in discharge rate and cortical receptive fields shifts were also associated with sleep.

Nevertheless, a great proportion ($\approx$50%) of cortical units presented no variations in the auditory evoked discharge during sleep, while there were no units that stopped firing on passing to sleep. Similar results apply both to the cortex and to the pathway nuclei.

Examples of four auditory pathway *loci* are shown in Figure 1, 293 neuronal firing were analyzed from the cochlear nucleus up to the primary cortex. The percentages of firing shifts are presented on passing from W to SWS and from SWS to PS, showing quantitative differences although including a set of auditory units that continue to fire as during W. The latter phenomenon was more marked at the cortical level (50% and 58% of the recorded neurons). Changes in the discharge pattern at the lateral superior olive and the inferior colliculus were also demonstrated by our group (see references).

### Sensory neurons showing hippocampal theta rhythm phase-locking

The hippocampal theta rhythm was recorded with bipolar electrodes in the CA1 region as well as the electromyogram and electrocorticogram for determining states of sleep and wakefulness. A small craniotomy over the different regions under study was made and left opened for glass micropipette penetration, protected with antibiotic and corticosteroid cream.

We analyzed the hippocampus field potential by waveform autocorrelation and power spectral analysis and the correlation between the theta rhythm and sensory units by spike-triggered averaging (cross-correlation). As a control, we performed a "shuffling" of the digitized unitary discharge. The cross-correlation was considered positive when the rhythm appears in the average and when calculated with the same data after "shuffling" the spikes series (interchanging the spike intervals at random) the average became flat.
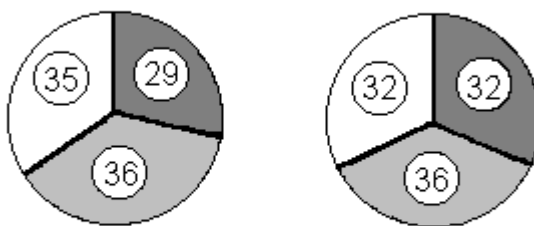
Cortical units were temporally correlated with the hippocampal theta rhythm (phase-locked) during W, SWS and PS. Auditory neurons from the inferior colliculus and the lateral superior olive were also phase-locked to the hippocampal theta rhythm.
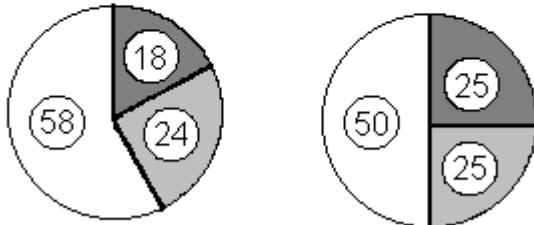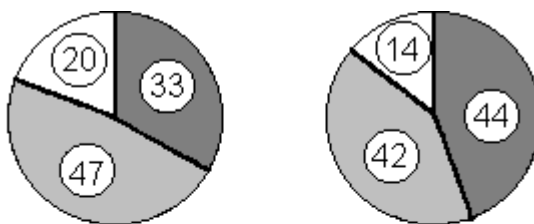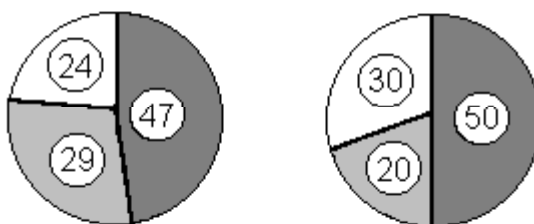
Figure 1. Neuronal evoked activity (*n*=293) along the auditory pathway during different behavioral states. Pie charts show percentage changes of neuronal firing on passing from wakefulness (W) to slow wave sleep (SWS), and from SWS to paradoxical sleep (PS), at four auditory regions: auditory cortex, inferior colliculus, lateral superior olive, and cochlear nucleus. No neurons have been recorded that became silent on passing to sleep at any level of the pathway. (Data from Peña *et al.*, 1992; Pedemonte *et al.*, 1994; Morales-Cobas *et al.*, 1995; Peña *et al.*, 1999).

Figure 2 shows an inferior colliculus auditory neuron with a theta rhythm phase-locking in W. Its spontaneous activity was phase-locked to hippocampal theta, exhibiting a high power spectrum (Fig. 2B) without rhythmicity in the spike autocorrelogram (Fig. 2C). The amplitude of the cross-correlation increased (becoming more synchronized) when the unit was stimulated with a continuous pure tone at the neuron characteristic frequency (Fig. 2A, evoked activity). The power spectrum showed no changes in the theta power (Fig. 2B, bottom) but, significantly, the spike firing became rhythmic in the autocorrelation (Fig. 2C, bottom); thus, the theta rhythm input may have enhanced its influence. Although the differences in the firing pattern, there was no significant increase in firing number (n=287 *vs* n=289) between the spontaneous activity and the sound evoked responses.

We have also studied the visual sensory modality at the thalamic level. Neuronal activity of the lateral geniculate body was recorded during sleep-waking cycle, and the unit firing was cross-correlated with hippocampal theta field activity.

Those temporal correlations between hippocampal theta and sensory neuronal firing were found both during W and sleep, appearing during brief periods, spontaneously or provoked by a change in the sensory input. The theta rhythm may be activated through several physiological variables, such as attention, movements, etc.; thus, the phase-locking could be also dependent on the one most relevant input at a particular time.
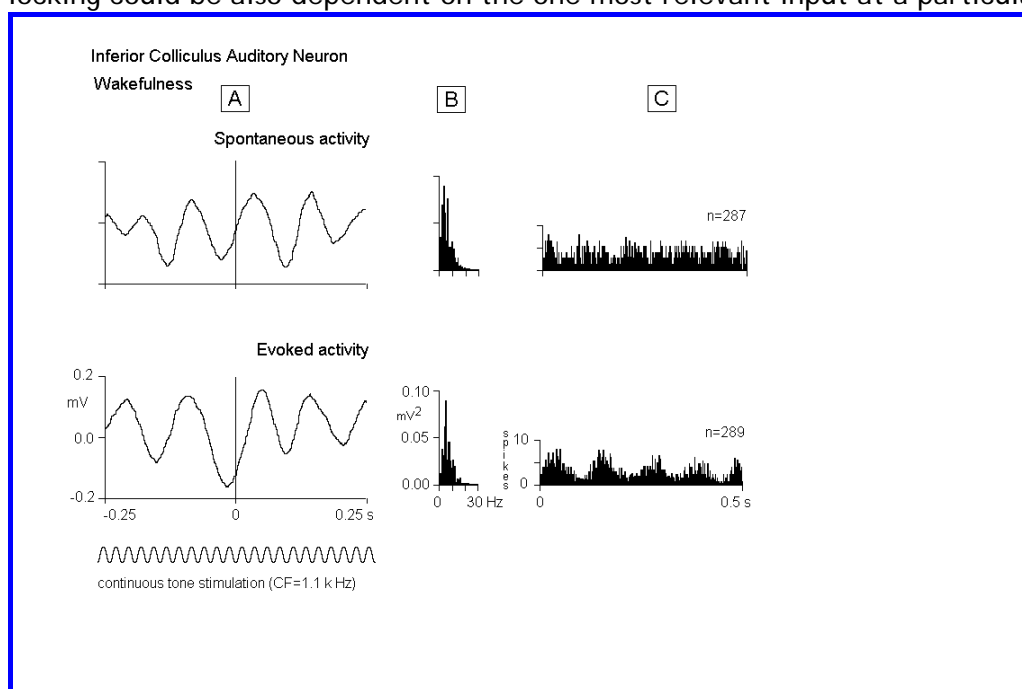

Figure 2. Temporal correlation between hippocampal theta rhythm and inferior colliculus neuronal discharge during wakefulness: A, cross-correlation between the neuron's firing and hippocampus field activity shows phase locking during both spontaneous and evoked discharge (sound stimulus: pure tone at the unit characteristic frequency, CF, 10 dB above threshold); B, hippocampus field activity power spectra; C, the autocorrelation histograms exhibit arrhythmic discharge during spontaneous activity that becomes rhythmic (at theta frequency) during the evoked activity. (Modified from, Pedemonte *et al.*, 1996).

Neurotransmitters at the inferior colliculus neurons in sleep and wakefulness

The third approach to understanding sensory processing was the study of neurotransmitters involved in the auditory pathway during sleep. We will present here the results obtained for excitatory amino acids in the inferior colliculus (IC). The IC is located in a key anatomical position where ascending auditory projections from lower nuclei and descending fibers from the cortex converge. Since IC is a synaptic crossroad of afferent and efferent projections its role may be to control the traffic of information through the pathway during behavioral states. Firing changes of IC central nucleus (ICc) and phase-locking to hippocampal theta have been reported during the sleep-waking cycle.

Glutamate receptors are present in IC and a glutamatergic cortical projection to IC has been described. A firing enhancement of ICc neurons was observed after the application of aspartate, glutamate, and the receptor agonist N-metyl-D-aspartate (NMDA). The iontophoretic application of 2-amino-5-phosphonovaleric acid (AP5) in anesthetized animals blocked the excitatory effect of NMDA, reducing the evoked and spontaneous firing in the central, external and lateral nuclei of IC.

In addition, the auditory efferent system exhibits a wide distribution of direct cortical efferent fibers into the ICc nucleus in rat and monkey that may influence the auditory input processing. Intracellular recordings showed excitatory and inhibitory synaptic potentials in ICc neurons in response to auditory cortical (AI) electrical stimulation in anesthetized and awake animals. Moreover, ipsilateral and contralateral stimulation of the auditory cortex evoked firing enhancement or depression in the same ICc neuron. In the bat's IC was described a corticofugal excitation of the external nucleus neurons that, in turn, may inhibit ICc neurons through GABAergic receptors.

Glutamate receptor blockers were applied to study the role of excitatory amino acids on the auditory input processing in physiological conditions, that is, in non-anesthetized animals. To achieve this goal, the excitatory amino acid neurotransmitter blockers AP5 and kynurenic acid (Kyn) were iontophoretically applied onto ICc neurons during the wakefulness-sleep cycle and after cortical electrical stimulation, using double-barreled micropipettes and bipolar stimulating electrodes on the surface of the primary auditory cortex. The NMDA channel-blocker AP5 produced decreases in the evoked firing of the majority of the neurons, although a minor group showed increases associated with sleep and W.

Figure 3 shows peri-stimulus time histograms (PSTHs) in W and SWS during the application of AP5. In W, a significant firing decrease was present 45s after AP5 ejection. A few minutes later, the animal spontaneously entered SWS while the same neuron increased its evoked discharge, as previously reported. Then, a second AP5 iontophoretic ejection, now during SWS, also provoked a marked firing decrement. Ninety seconds after

stopping AP5 ejection, the guinea pig still was in SWS, while the firing number was about at the W level.

The action of Kyn acid, on the other hand, was compared with cortical (AI) electrical stimulation in ICc neurons during wakefulness (n=11). Both, the action of cortical electrical stimulation and Kyn acid iontophoretic ejection onto the same target ICc neuron in awake guinea pigs provoked a very similar (86% and 88% of the neurons respectively) and significant decrease in the unit discharge (p< 0.05).
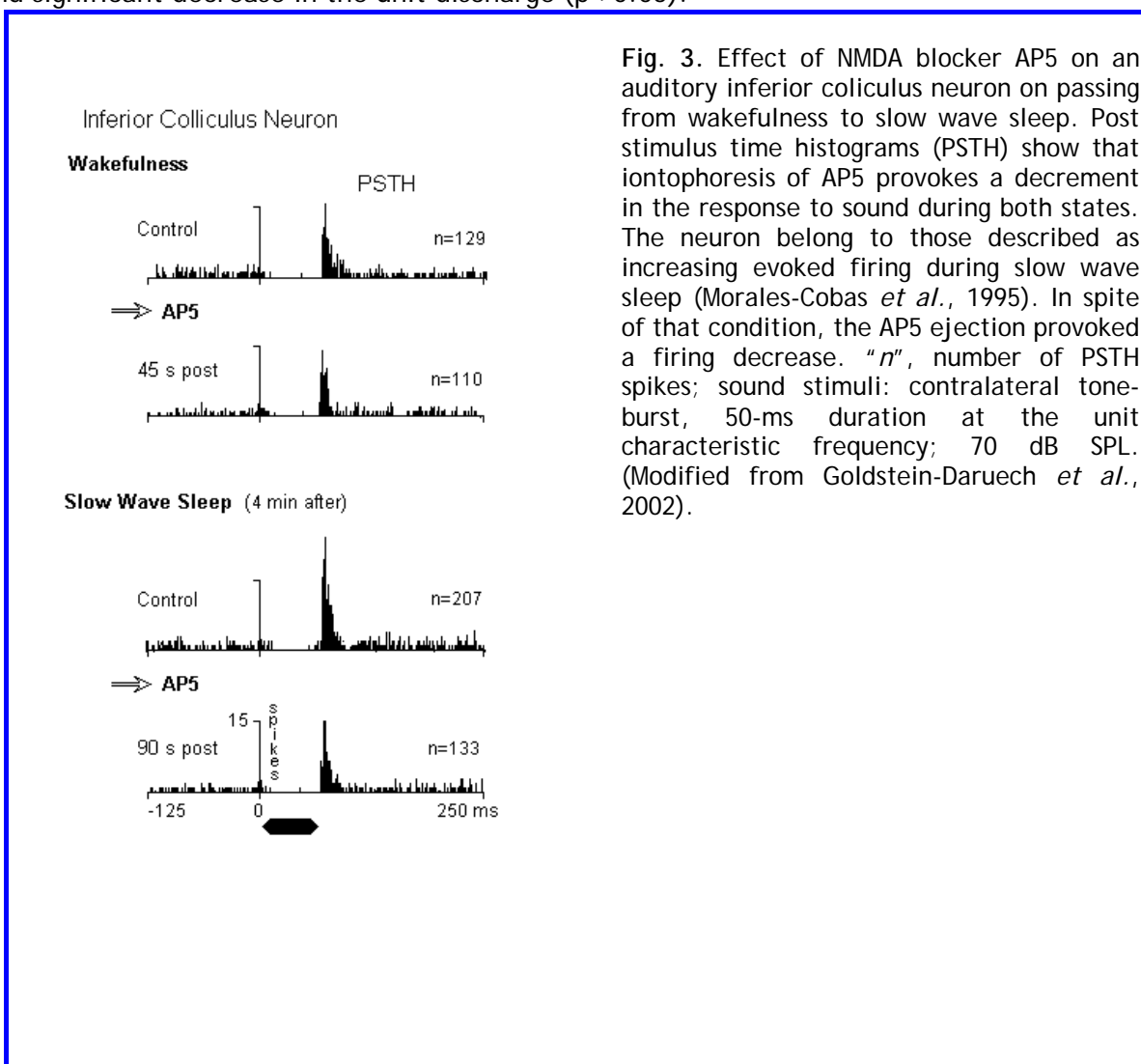

Fig. 3. Effect of NMDA blocker AP5 on an auditory inferior coliculus neuron on passing from wakefulness to slow wave sleep. Post stimulus time histograms (PSTH) show that iontophoresis of AP5 provokes a decrement in the response to sound during both states. The neuron belong to those described as increasing evoked firing during slow wave sleep (Morales-Cobas *et al.*, 1995). In spite of that condition, the AP5 ejection provoked a firing decrease. "*n*", number of PSTH spikes; sound stimuli: contralateral tone-burst, 50-ms duration at the unit characteristic frequency; 70 dB SPL. (Modified from Goldstein-Daruech *et al.*, 2002).

GENERAL DISCUSSION AND CONCLUSIONS

The three experimental approaches assess different aspects of sensory incoming unitary signals that may participate in the processing. Our conclusions are:

I) The neuronal discharge level and pattern changes in response to constant stimuli represent a way to show that the CNS is able to modulate the incoming auditory information according to the CNS state, including at the auditory nerve level. Thus, the auditory, somatosensory, and visual neurons studied exhibit changes in their firing rates in

correlation with stages of sleep and wakefulness. This is consistent with the hypothesis that a general shift in the function of the neuronal networks involved in sensory processing occurs during sleep. A number of the neurons at different auditory *loci*, from brain stem to the cortex itself, exhibited significant quantitative/qualitative changes in their evoked firing rates and pattern. These changes could be correlated with sleep stages or wakefulness from 42% to 80% of the sampled neurons throughout the pathway. Another neuronal population, recorded at every pathway nucleus and the cortex, did not show behavioral related changes in firing rates on passing to sleep, and no unit was noted to stop its firing on passing to sleep.

Our results indicate that the responsiveness of the auditory system during sleep can be considered at least partially preserved. This could be accomplished by the response of those neurons that continue to fire equally to the firing during W (about 50% at the primary cortical level), while for the remaining units that increase or decrease their evoked discharge, we postulate them to be participants also in sleep functions, perhaps associated to other neuronal networks, without knowing what their involvement in sleep neurophysiology could be.

II) A close temporal correlation between hippocampal θ rhythm and unitary firing was demonstrated at several stages in the auditory pathway and in visual neurons in the thalamic lateral geniculate. At a neural population scale, this phase locking may result in a composite final signal that could be used in processes like attention, movements, and, in particular auditory sensory input processing. Furthermore, we hypothesize that the phase locking to the hippocampal theta adds a temporal dimension to the sensory processing, perhaps necessary for time related perception. Given that every stimulus develops in time, the CNS must have a mechanism to encode this parameter. Hippocampal theta, being one of the most regular brain-generated low frequency rhythms, may participate in this internal clock.

The temporal relationship between the sensory neuronal firing and the hippocampal θ field activity is a changing phenomenon in the time domain whose variation may be dependent on the interaction of a set of signals: a) the hippocampal theta rhythm amplitude and frequency, b) the actual state of the brain, awake or asleep, and c) the incoming sensory information. A neuronal network may shift its discharge pattern by changing the interaction between these three input signals, e.g., facing a novel stimulus may shift the brain condition and evoke a new phase-locking by a higher power of hippocampal theta.

The parallel recording of hippocampal theta field activity and cortical auditory multiunit firing revealed a precise temporal organization of population events during W and both sleep phases, SWS and PS. Our results support the hypothesis of a discontinuous exchange of information between hippocampus and cortical areas, because the phase-

locking of cortical auditory units and hippocampal theta mainly occurs when a novel stimulus or repetition of the same one are applied during W, SWS and PS.

III) The analysis of the neurotransmitter roles in the auditory pathway, particularly in the IC in sleep and W can also contribute to the understanding of neural information processing. The results reported address the afferent and efferent actions in which excitatory neurotransmission is involved. In reference to NMDA action, it can be concluded that there are no differences, at the cellular level, between sleep and waking. Thus, other types of excitatory neurotransmission, as well as synaptic inhibition, may underlie the physiologically complex changes that occur in the sleeping brain.

The excitatory efferent system was postulated as being mainly glutamatergic. Thus, the effect of auditory (AI) electrical stimulation was mimicked, a few minutes later, by iontophoretic Kyn ejection onto the same IC neuron, supporting the notion of an efferent path acting through excitatory amino acid receptors on IC cells and/or on inhibitory neurons.

The descending auditory system could participate in the processing of the incoming information. Excitatory amino acid transmission would be present in sleep and wakefulness, acting by similar mechanisms together with several other neurotransmitters acting on the same neuron.

IV) Corollaries of the finding that auditory unitary input and its hippocampus theta phase-locking persist during sleep, are that: a) the neurons that keep responding during sleep- as well as those units that exhibit theta phase-locking- may convey information that could be learned. This is consistent with a recent report of learning during sleep in human newborns. b) the activity-dependent development of the brain during early life may not only occur during wakefulness, but we suggest that it may also occur during the long periods of sleep in newborns and infants. Thus, during early ontogenetic development, and maybe in adults, the sensory information that reaches the CNS during sleep may be "sculpting" the brain.

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