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Principal cell types of sleep–wake regulatory circuits

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Electrophysiological recordings indicate that neurons which discharge maximally in association with distinct sleep–wake states are distributed through the brain, albeit in differing proportions. As studied using juxtacellular recording and labeling within the basal forebrain, four functional principal cell types are distinguished as: wake/paradoxical sleep (W/PS)-, slow wave sleep (SWS)-, W- and PS-max active. They are each comprised by both GABA and glutamate neurons, in addition to acetylcholine neurons belonging to the W/PS group. By their discharge profiles and interactions, the GABA and glutamate neurons of different groups are proposed to have the capacity to generate sleep–wake states with associated EEG and EMG activities, though to also be importantly regulated by neuromodulatory systems, each of which belong to one functional cell group.

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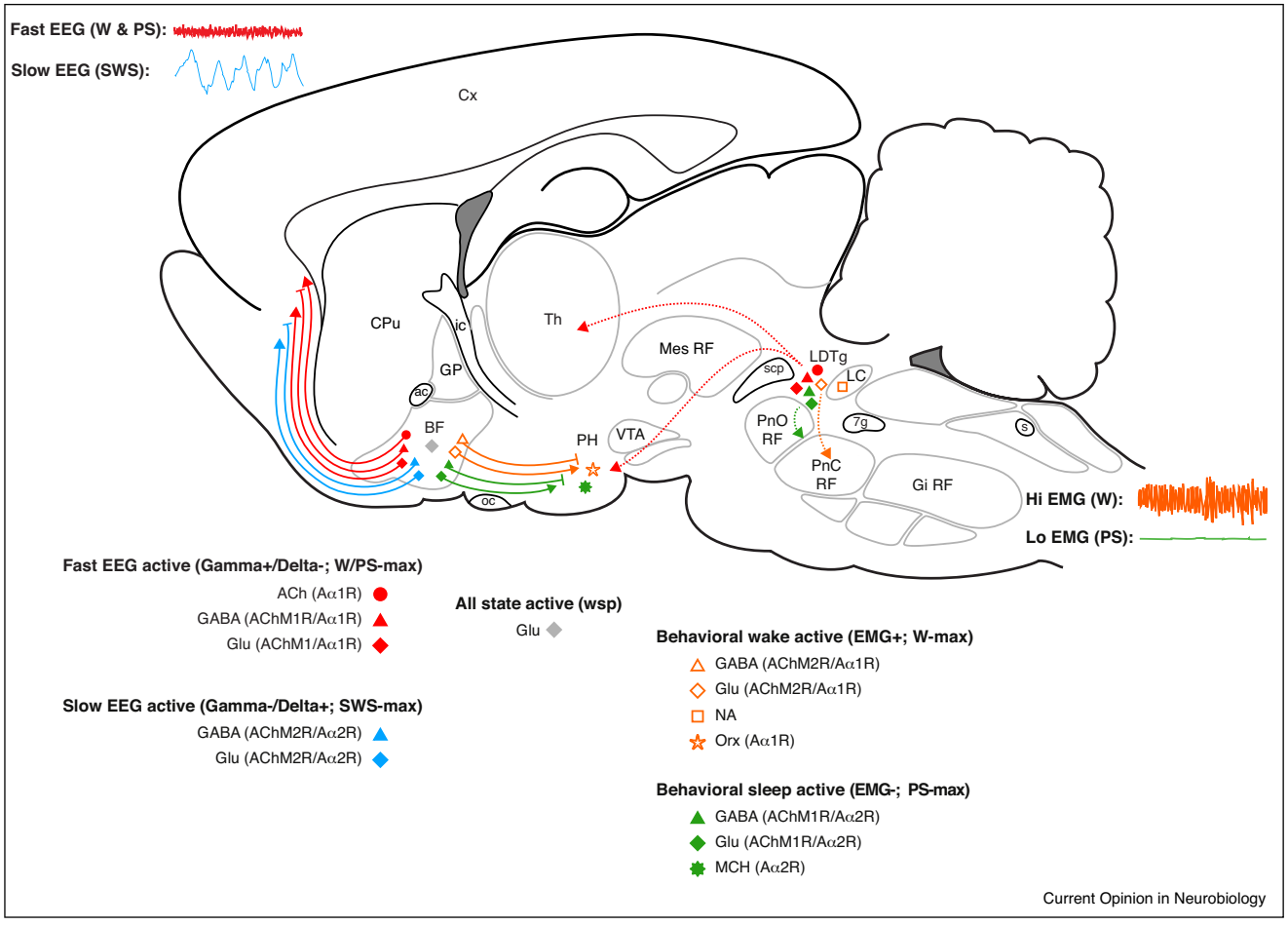
Introduction

Over the last century the principal regions and chemical modulators of sleep–wake systems in the brain were identified through application of lesion, stimulation and pharmacological approaches in association with chemical neuroanatomical study (see for review, Ref. [1]). Yet, only recently have the principal cell types of these regions been distinguished using electrophysiological recordings of chemically identified neurons to fully characterize their discharge profiles and thereby understand how they can regulate sleep–wake states, as will be presented in this review (Figure 1).

From early studies of the effects of lesions in humans and experimental animals (see for review, Ref. [2]), the generation of sleep and wake states was attributed to different regions of the brain: sleep to the anterior hypothalamus, preoptic area and basal forebrain (BF) and wake to the posterior hypothalamus (PH) and brainstem reticular formation (RF) (Figure 1). Yet, within these regions, electrical stimulation could elicit different states depending upon the frequency of the stimulation: slow, eliciting slow wave electroencephalogram (EEG) activity with sleep and fast, eliciting fast EEG activity with wake along with elevated postural muscle electromyogram (EMG) (Figure 1), suggesting that the same neurons would drive different EEG activities and states or that different neurons within the same region would drive different EEG activities and states. In the thalamus, where specific sensory-motor relay and nonspecific projection neurons transmit inputs from the periphery and brain to the cerebral cortex, recording studies indicated that the same neurons would influence cortical activity and state by different patterns of slow vs. fast activity during naturally occurring slow wave sleep (SWS) and wake (W) (see for review, Ref. [3]). Yet within the brainstem, hypothalamus, preoptic area and BF areas, unit recording studies indicated that different neurons discharged more selectively during different states [3]. Accordingly in these regions, specific neuronal cell groups were thought to be responsible for the three major states of W, SWS and rapid eye movement sleep (REMS) or as was originally called in animals according to its essential character by Jouvet, paradoxical sleep (PS), as employed here (Figure 1). In the forebrain, neurons which discharged relatively selectively during SWS and/or PS, as sleep-active neurons, were recorded in the BF and preoptic area [4,5]. In the PH and brainstem RF, W-active neurons whose discharge was correlated with EEG or behavioral correlates of waking and EMG were recorded [6–8]. And in different regions of the brainstem, neurons which discharged relatively selectively during PS were identified (see for review, Ref. [3]).

Pharmacological studies along with chemical neuroanatomical and lesion studies subsequently revealed the very important and ostensibly state-selective roles of neuromodulatory systems, notably the monoamine and acetylcholine (ACh) containing neurons, in sleep–wake states (see for review, Ref. [9]). Yet to fully understand the way in which each of these specific systems could actually regulate or modulate sleep–wake states, it was necessary to know the way in which the specific neurons discharged in relation to the sleep–wake states. With the discrete localization of the noradrenaline (NA) neurons in the locus coeruleus (LC) nucleus (Figure 1) for which extensive evidence indicated an important role in W, it was

Figure 1



Schematic sagittal diagram of the rat brain showing principal cell types of the sleep–wake regulatory circuits. Three distinct sleep–wake states of wake (W), slow wave sleep (SWS) and paradoxical sleep (PS) are associated with distinct electroencephalogram (EEG, upper left) and electromyogram (EMG, lower right) activities which are in turn regulated by four functionally distinct cell groups according to their discharge profiles and major long projections: W/PS-max active (red), SWS-max active (blue), W-max active (orange) and PS-max active (green) in addition to state-indifferent wsp (gray) neurons, as recorded with the juxtacellular technique and fully characterized in the basal forebrain (BF) and also in the pontomesencephalic tegmentum and posterior hypothalamus (PH). Cells depicted were all identified according to their neurotransmitter. Based upon *in vivo* and *in vitro* pharmacological studies, the different neurons are assumed to bear particular receptors (R) for ACh (muscarinic, M) or NA (adrenergic, A), which are associated with excitation (AChM1R; Aα1R) or inhibition (AChM2R; Aα2R). Abbreviations: 7g, genu 7th nerve; ac, anterior commissure; ACh, acetylcholine; BF, basal forebrain; CPu, caudate putamen; Cx, cortex; EEG, electroencephalogram; EMG, electromyogram; Gi RF, gigantocellular RF; Glu, glutamate; GP, globus pallidus; ic, internal capsule; LC, locus coeruleus nucleus; LDTg, laterodorsal tegmental nucleus; MCH, melanin concentrating hormone; Mes RF, mesencephalic RF; NA, noradrenaline; oc, optic chiasm; Orx, orexin; PH, posterior hypothalamus; PnC RF, pontine, caudal part RF; PnO RF, pontine, oral part RF; PS, paradoxical sleep; RF, reticular formation; s, solitary tract; scp, superior cerebellar peduncle; SWS, slow wave sleep; Th, thalamus; VTA, ventral tegmental area; W, wake.

possible to record specifically from those NA neurons and learn that they discharge selectively during W, as W-active neurons, and become silent during sleep, to be off during PS [10,11].

On the other hand, the activity of ACh neurons could not be recorded with any certainty, since they lie intermingled with large numbers of noncholinergic, including GABA and glutamate (Glu), neurons in the BF [12] (Figure 1). Like the ACh neurons, BF GABA and Glu neurons project to the cerebral cortex [13]. Other GABA and Glu neurons project caudally to the PH and perhaps beyond [14]. Given this chemical and hodological, along with apparent functional heterogeneity of the BF cell population, it was essential to be able to record from chemically identified cells in order to determine the specific discharge properties and profiles of the ACh, GABA and Glu BF neurons.