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PHYSIOLOGICAL REVIEW

Not a single but multiple populations of GABAergic neurons control sleep

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SUMMARY

The role of gamma-amino butyric acid (GABA) in sleep induction and maintenance is well accepted since most insomnia treatments target GABAa receptors. However, the population(s) of GABAergic neurons involved in the beneficial effect of GABA on sleep remains to be identified. This is not an easy task since GABAergic neurons are widely distributed in all brain structures. A recently growing number of populations of GABAergic neurons have been involved in sleep control. We first review here possible candidates for inducing non-rapid eye movement (NREM) sleep including the GABAergic neurons of the ventrolateral preoptic area, the parafacial zone in the brainstem, the nucleus accumbens and the cortex. We also discuss the role of several populations of GABAergic neurons in rapid eye movement (REM) sleep control. Indeed, it is well accepted that muscle atonia occurring during REM sleep is due to a GABA/glycinergic hyperpolarization of motoneurons. Recent evidence strongly suggests that these neurons are located in the ventral medullary reticular formation. It has also recently been shown that neurons containing the neuropeptide melanin concentrating hormone and GABA located in the lateral hypothalamic area control REM sleep expression. Finally, a population of REM-off GABAergic neurons located in the ventrolateral periaqueductal gray has been shown to gate REM sleep by inhibiting glutamatergic neurons located in the sublaterodorsal tegmental nucleus. In summary, recent data clearly indicate that multiple populations of GABAergic neurons located throughout the brain from the cortex to the medulla oblongata control NREM and REM sleep.

Introduction

In most mammals, three vigilance states can be characterized based on electroencephalogram (EEG), electromyogram (EMG) and electro-oculogram (EOG) recordings. The waking state (W) is characterized by higher-frequency (40–300 Hz), low-amplitude (desynchronized) EEG activity, sustained EMG activity and ocular movements; non-rapid eye movement (NREM) sleep, also named slow wave (SWS) sleep (synchronized), is characterized by the presence of low-frequency (0.5–4 Hz), high-amplitude delta oscillations and spindles (14 Hz) on the EEG, low EMG muscular activity and absence of ocular movements; and rapid eye movement (REM) sleep, also called paradoxical sleep (PS), is characterized by a predominant theta (6–9 Hz) and gamma (30–300 Hz) rhythms similar to the waking EEG, a complete disappearance of postural muscle tone and the occurrence of rapid eye movements (REMs) and muscle twitches. Below, we review evidence linking GABAergic neurons with both NREM and REM sleep.

The strong historical link between GABA and sleep

Still today, most treatments for insomnia target GABAergic transmission. The first used drugs were barbiturates synthesized in 1864 by Adolf von Baeyer. These drugs increase the binding of gamma-amino butyric acid (GABA) to GABAa receptors. They were shown to induce sleep in the early twentieth century. More precisely, it was shown that they increase NREM sleep duration and inhibit REM sleep [1]. Further, they promote spindles and decrease delta activity [2]. The next generation of hypnotics, the benzodiazepines (diazepam, flunitrazepam, flurazepam, triazolam and midazolam) appeared in the 1960s. They became very popular because of their strong anxiolytic and hypnotic properties. Further, they exhibited less toxicity compared to barbiturates with a lower

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Nomenclature

A_1R	adenosine A1 receptors
$A_{2A}R$	adenosine A2 receptors
CTb	cholera toxin b subunit
dDpMe	dorsal deep mesencephalic reticular nucleus
DPGi	dorsal paragigantocellular reticular nucleus
DREADD	designer receptors exclusively activated by designer drugs
DRN	dorsal raphe nucleus
EEG	electroencephalogram
EMG	electromyogram
GABA	γ-amino butyric acid
GABAa	GABAergic receptor, type a
GABAb	GABAergic receptor, type b
GAD	glutamate decarboxylase
GAD67 mRNA	mRNA for the enzyme of synthesis of GABA
GHB	gamma-hydroxybutyrate
GiA	alpha gigantocellular reticular nucleus
GiV	ventral gigantocellular reticular nucleus
ICV	intracerebroventricular
LC	locus coeruleus
Ldt	laterodorsal tegmental nucleus
LHA	lateral hypothalamic area
LPGi	lateral paragigantocellular reticular nucleus
MCH	melanin concentrating hormone
MnPn	median preoptic nucleus
NA	noradrenalin
nNOS	nitric oxide synthase
NREM	non-rapid eye movement
PeF	perifornical area
peri-LCα	nucleus peri-locus coeruleus alpha
PH	posterior hypothalamus
POA	preoptic area
PPT	pedunculopontine nucleus
PS	paradoxical sleep
PZ	medullary parafacial zone
REM	rapid eye movement
REM-on	neuron specifically active during REM sleep
REM-off	neuron specifically silent during REM sleep
RMg	nucleus raphe magnus
RT	reticular thalamus nucleus
SLD	sublaterodorsal tegmental nucleus
SubC	subcoeruleus nucleus
SWS	slow wave sleep
TH	tyrosine hydroxylase
TMN	tuberomammillary nucleus
vlPAG	ventrolateral periaqueductal gray
VLPO	ventrolateral preoptic nucleus
W	waking
ZI	zona incerta

risk of overdose, although they still engendered tolerance and serious withdrawal effect [3]. Benzodiazepines bind to the GABAa receptor complex (at the interface of the α1, α2, α3 or α5 and the γ2 subtype) and enhance the affinity of GABA for its receptor [3]. They are positive allosteric modulators, enhancing the GABA-induced chloride current by facilitating the frequency of ion channel openings. They have no effect in the absence of GABA. Benzodiazepines shorten sleep onset latency, increase sleep continuity and inhibit REM sleep [4]. They increase spindles and stage 2 of NREM sleep at the expenses of delta and stage 3 but do not abolish the progressive decrease of slow wave power across the night [4]. These modifications persist over the following drug-free night. The side-effects of benzodiazepines such as next-day sedation, cognitive impairment and amnesia have led to the emergence of a third generation of hypnotics named the Z-drugs like the imidazopyridines, the pirazolopyrimidines and the cyclopyrrolones. These drugs are structurally different from benzodiazepines but they bind on the same site of the GABAa receptors. They nevertheless display a higher binding affinity to α1 than to α2, α3 and no binding to α5 subtype. It has been shown that neurons expressing α1 subtype mediate sedation, whereas those expressing α2 subtype mediate anxiolysis [5]. Globally, these compounds show similar actions on sleep as benzodiazepines such as shortened sleep latency and a dose-dependent reduction in REM sleep [6]. They also induce an increase in spindles and a decrease in delta activity. Importantly, the increase in delta power after total sleep deprivation is preserved with these compounds and the benzodiazepines [6,7].

In summary, increasing GABAergic transmission through the GABAa receptors induces three types of effects on sleep:

1) An increase in spindles (stage 2 of NREM sleep) and a decrease in delta activity (stage 3 of NREM sleep).
2) A shortened sleep onset latency and an increase in sleep continuity
3) An inhibition of REM sleep

These data unequivocally demonstrate that GABAa transmission plays key roles in sleep and sleep pathologies such as insomnia. Interestingly, the suppression of delta waves by diazepam was decreased in mice harboring diazepam-insensitive α2 GABAa receptors but not in those with diazepam-insensitive α1 and α3 GABAa receptors [8–10]. The α1 and α3 GABAa receptors are predominant in the thalamo-cortical network, whereas α2 receptors are practically absent in the thalamus and are expressed in hypothalamic and pontine nuclei [11]. These results suggest that the effect of benzodiazepines on delta activity may be mediated by an increase in GABAergic transmission in subcortical structures controlling the thalamo-cortical network rather than on reticular thalamic or neocortical GABAergic neurons.

In addition to the role of GABAa receptors, an increasing number of studies highlight the role of GABAb receptors in sleep. It was first shown that the GABAb agonist baclofen increases sleep and promotes delta waves [12]. In addition, gama-hydroxybutyrate (GHB), a GABA metabolite known to bind to GABAb receptors, decreases sleep latency and promotes deep NREM sleep [13]. Animal studies showed that GHB or baclofen administration induces EEG slow wave activity [14]. Sodium oxibate, a formulation of GHB, is also used as an effective treatment for narcolepsy, promoting sleep quality and decreasing cataplexy [15].

In order to treat sleep pathologies more efficiently, it seems crucial to determine which GABAergic neuronal populations mediate the effects of GABA on sleep. This is a difficult task since GABAergic neurons are localized in nearly all brain structures from the neocortex to the spinal cord. It seems, therefore, unlikely that a single population of GABAergic neurons mediates all the effects listed above.

In the following sections, based on the extensive published literature and our work, we present and discuss the different