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Selective targets for arousal-modifying drugs: implications for the treatment of sleep disorders

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The level of arousal reflects the interaction between wakefulness-promoting and sleep-promoting nuclei located in the hypothalamus and brainstem. The nuclei and their connections constitute the sleep–arousal network. Mapping out this network, together with the neurotransmitters involved, has created a unique opportunity for the design of drugs for sleep disorders–it has become possible to target specific sites within the network with predictable effects on the level of arousal. Recent examples of this approach are orexin receptor and $5HT_{2A}$ serotonin receptor antagonists and melatonin receptor agonists for the treatment of insomnia, and H3 histamine receptor antagonists for the treatment of excessive daytime sleepiness.

Introduction

A simple classification of sleep disorders distinguishes between insomnia (lack or inadequate amount of sleep), hypersomnia [excess of sleep, including excessive daytime sleepiness (EDS)] and parasomnia (behavioural disturbance associated with sleep [1]. A more comprehensive modern classification system (international classification of sleep disorders; ICSD-2) includes five further categories: circadian rhythm sleep disorders; sleep-related breathing disorders; sleep-related movement disorders; isolated symptoms and normal variants; other sleep disorders [2].

The traditional approach to the treatment of sleep disorders, in particular of insomnia and/or hypersomnia, was based on the view that arousal reflected the general level of excitability of the brain. The aim was to shift the level of neuronal excitability along the maximum sedation (coma)–maximum excitation (convulsions) continuum, where each level of central nervous system (CNS) activity could be defined in terms of the dominant frequency in the electroencephalogram (EEG) [3]. Drugs that shifted the level of arousal in either direction were regarded as nonselective, drugs that depressed the activity of all neurons (general CNS depressants) were sedative and drugs that enhanced the activity of all neurons (general CNS stimulants) were alerting [4]. However, this view has been superseded by the more recent discovery that arousal-modulating drugs act at specific well-defined sites in the brain. The basis of this discovery was the mapping out of the sleep–arousal neuronal network, consisting of interconnected and interacting wake-promoting and sleep-promoting nuclei in the hypothalamus and the brainstem (see below).

It is possible to distinguish between three states of arousal (or vigilance states, also referred to as behavioural states) [5]: wakefulness, characterised by fast, small-amplitude, desynchronised EEG, active muscle tone and conscious awareness; slow-wave sleep [non-rapid-eye-movement (REM) sleep], characterised by synchronised, slow, large-amplitude EEG, reduced muscle tone, lack of conscious awareness; REM sleep (paradoxical or active sleep), characterised by fast, desynchronised EEG, loss of muscle tone and variable levels of conscious awareness [6,7]. The three vigilance states and the transitions between them are regulated by the subcortical sleep–arousal network (see below). During slow-wave sleep the cerebral cortex displays its synchronised intrinsic activity; wakefulness ensues when this 'cortical soliloquy' is disrupted by afferent inputs from subcortical wake-promoting areas located in the diencephalon and the brainstem [7]. It has been suggested that the main function of the subcortical sleep-promoting neurons is to switch off the wake-promoting neuronal groups and allow slow-wave sleep to develop [7].

The sleep–arousal network

The sleep–arousal network consists of distinct wake-promoting and sleep-promoting nuclei, and their connections, located in the basal

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1359-6446/06/$ - see front matter © 2014 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.drudis.2014.01.001

Please cite this article in press as: E. Szabadi, Selective targets for arousal-modifying drugs: implications for the treatment of sleep disorders, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.01.001

forebrain (BF – medial septal nucleus, diagonal band of Broca, *substantia innominta*), diencephalon [thalamus (Th) and hypothalamus] and the brainstem. The wake-promoting and sleep-promoting nuclei show opposite and reciprocal activities during wakefulness and sleep – the wake-promoting nuclei are active during wakefulness, show reduced activity during slow-wave sleep and are quiescent during REM sleep, whereas the sleep-promoting nuclei are active during slow-wave sleep and quiescent during wakefulness [6–9]. A notable exception is the wake-promoting dopaminergic neurons of the ventral tegmental area (VTA) where the firing rate does not change across the sleep–wakefulness cycle – these neurons fire in bursts during wakefulness and REM sleep [10].

A partially overlapping network is responsible for the regulation of the vigilance state involving REM sleep. This network comprises complex interactions between GABAergic, glutamatergic and cholinergic neurons in the brainstem [5,11]. The interactions between these neuronal groups in the generation of REM sleep have been incorporated into several models of neuronal organisation such as the reciprocal interaction model [12], the 'flip–flop' circuit model [13] and the revised model of REM sleep control [14]. For reviews on the comparison of different models of REM sleep generation, see [15,16].

A schematic diagram of the sleep–arousal network is shown in Fig. 1. Wake-promoting nuclei are located in the BF, the diencephalon and the brainstem. The BF contains a population of excitatory wake-promoting cholinergic neurons projecting to the cerebral cortex [7,17]. These neurons have been implicated in relaying wake-promoting information from the histaminergic neurons of the tuberomamillary nucleus (TMN) [18] and the noradrenergic neurons of the locus coeruleus (LC) [19] to the cortex. Excitatory glutamatergic and inhibitory GABAergic neurons are also present in the BF and project to the cerebral cortex [20]. Whereas the glutamatergic neurons are wake-promoting, the GABAergic neurons form a mixed population including wake-promoting and sleep-promoting neurons. Some of the GABAergic neurons of the BF are believed to synapse with inhibitory interneurons in the cerebral cortex – by switching off the activity of these neurons they stimulate cortical activity and thus exert a wake-promoting effect. By contrast, some other GABAergic BF neurons synapse with principal cortical neurons. By inhibiting the activity of these neurons they suppress cortical activity and thus exert a sleep-promoting effect [20]. Interestingly, it has been shown that a noradrenergic input to the BF from the LC exerts a dual effect on different neuronal populations; whereas wake-promoting cholinergic neurons of the BF are excited via the stimulation of α_1-adrenoceptors, sleep-promoting GABAergic neurons are inhibited via the stimulation of α_2-adrenoceptors [21]. In the diencephalon wake-promoting neuronal groups include the glutamatergic neurons of the medial and intralaminar nuclei of the Th [6,7], the histaminergic neurons of the TMN of the hypothalamus and the orexinergic neurons of the lateral hypothalamic–perifornical area (LH–PF) [9]. Wake-promoting nuclei in the brainstem are the noradrenergic LC [22], the serotonergic dorsal raphe nucleus (DR) [23], the dopaminergic neurons of the periaqueductal grey (PAG) and the ventral tegmental area (VTA) [10,24], and some

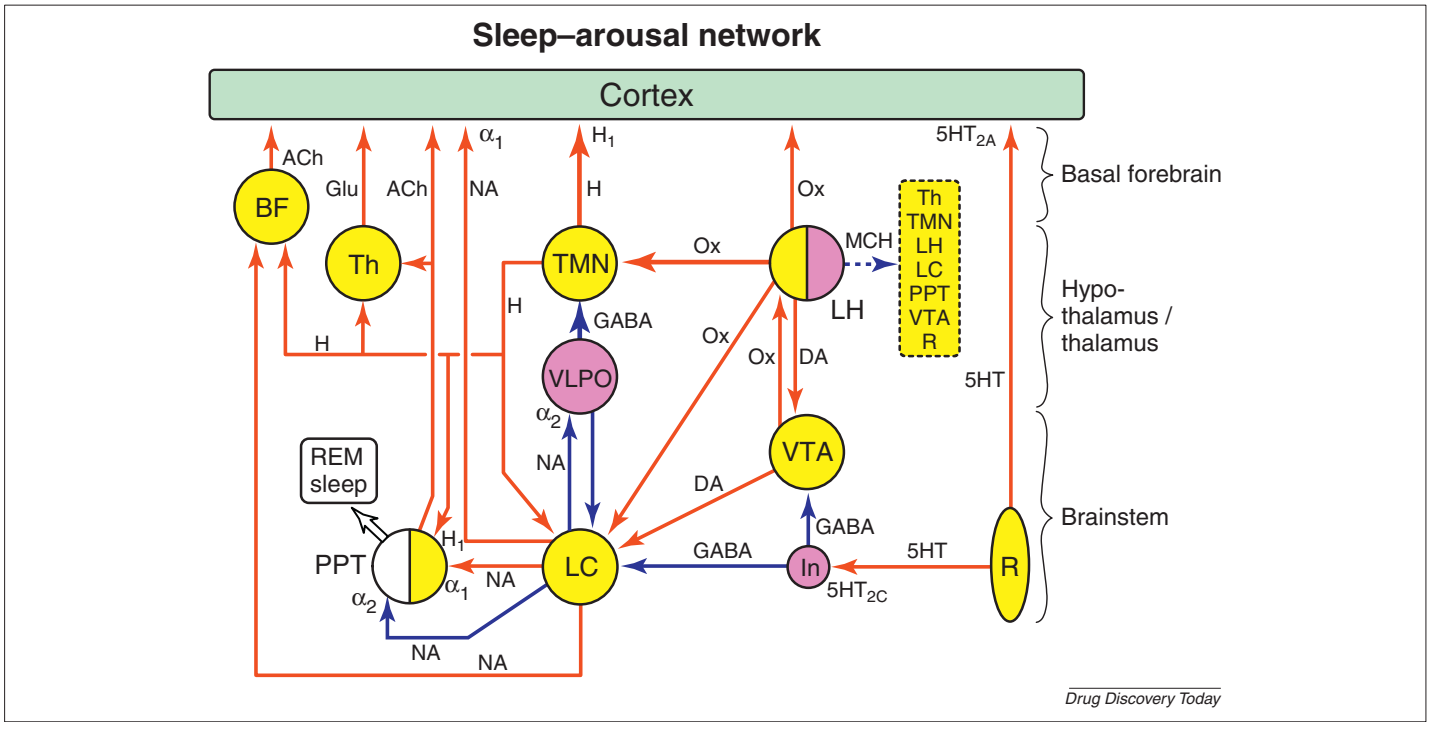

FIGURE 1

Schematic diagram of the sleep–arousal network. Wakefulness-promoting nuclei (yellow): BF, basal forebrain; TMN, tuberomamillary nucleus; LH, lateral hypothalamic area; Th, thalamus; LC, locus coeruleus; VTA, ventral tegmental area; PPT, pedunculopontine tegmental nucleus; R, raphe nuclei. Sleep-promoting nuclei (purple): VLPO, ventrolateral preoptic nucleus; in, GABAergic interneurons; LH, lateral hypothalamic area. REM-sleep-promoting nucleus (white): PPT, pedunculopontine tegmental nucleus. Neurotransmitters: ACh, acetylcholine; NA, noradrenaline; H, histamine; Ox, orexin; GABA, γ-aminobutyric acid; DA, dopamine; 5HT, 5-hydroxytryptamine; Glu, glutamate; MCH, melanin-concentrating hormone. Receptors: α_1, excitatory α_1-adrenoceptors; α_2, inhibitory α_2-adrenoceptors; H_1, excitatory H_1 histamine receptors; $5HT_{2A}$ and $5HT_{2C}$, excitatory 5HT receptors. Neuronal outputs: excitatory (red arrows); inhibitory (blue arrows). See text for details. Modified, with permission, from [6].

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