Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Control of arousal by the orexin neurons

Chloe Alexandre[1], Mark L Andermann[2] and Thomas E Scammell[1]

The orexin-producing neurons in the lateral hypothalamus play an essential role in promoting arousal and maintaining wakefulness. These neurons receive a broad variety of signals related to environmental, physiological and emotional stimuli; they project to almost every brain region involved in the regulation of wakefulness; and they fire most strongly during active wakefulness, high motor activation, and sustained attention. This review focuses on the specific neuronal pathways through which the orexin neurons promote wakefulness and maintain high level of arousal, and how recent studies using optogenetic and pharmacogenetic methods have demonstrated that the locus coeruleus, the tuberomammillary nucleus, and the basal forebrain are some of the key sites mediating the arousing actions of orexins.

Addresses
[1] Department of Neurology, Beth Israel Medical Deaconess Center, Boston, MA 02215, United States
[2] Division of Endocrinology, Department of Medicine, Beth Israel Medical Deaconess Center, Boston, MA 02215, United States

Corresponding author: Scammell, Thomas E (tscammel@bidmc.harvard.edu)

Current Opinion in Neurobiology 2013, **23**:752–759

This review comes from a themed issue on **Circadian rhythm and sleep**

Edited by **Clifford Saper** and **Amita Sehgal**

For a complete overview see the Issue and the Editorial

Available online 15th May 2013

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.04.008

Introduction

Survival depends on an animal's ability to stay awake and dynamically adjust its arousal level to meet environmental and physiological demands. Wakefulness is characterized behaviorally by consciousness, voluntary motor activation, and high responsiveness to environmental stimuli, and electrophysiologically by general activation of the cerebral cortex and increased neuronal excitability. Though often referred to as a single state, wakefulness encompasses many interdependent neuropsychological components, including arousal, awareness, attention, memory, motivation and emotions [1].

Arousal is the overall level of responsiveness of an animal, often measured by the degree of stimulation necessary to trigger a specific response [2]. High levels of arousal, for example caused by stimulating an animal with novel sensory stimuli, promote wakefulness [3]. In contrast, low arousal, such as the drowsiness caused by sleep deprivation or sedative medications, promotes transition to sleep and impairs performance and learning [4,5]. Maintenance of an adequate level of arousal is thus critical to trigger or sustain appropriate behavioral responses to the current environmental and internal conditions.

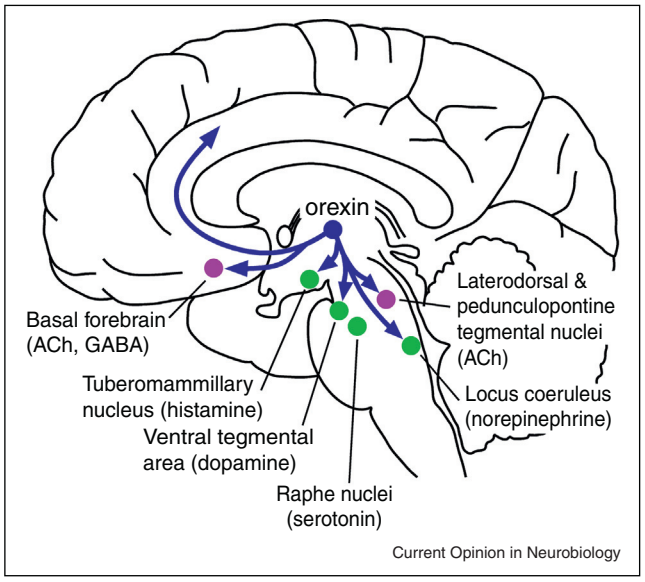
A variety of neurons promote arousal, and among these, the orexin-producing neurons are essential to promote stable periods of wakefulness and to sustain the alertness required for the expression of motivated behaviors. This review focuses on the neuronal pathways through which the orexin neurons promote wakefulness and help drive high levels of arousal.

Brief overview of the orexin system

The orexin neuropeptides were discovered simultaneously by two independent research groups [6,7], one of which named them orexins and the other hypocretins; the terms are used interchangeably in the literature. Orexin-A and orexin-B (hypocretin-1 and hypocretin-2) are synthesized by a cluster of neurons in the lateral hypothalamus and produce excitatory effects on target neurons. The orexin-producing neurons also synthesize glutamate and the inhibitory neuropeptide dynorphin, though the physiologic importance of these cotransmitters remains to be defined [8,9,10••]. The orexin neurons receive a broad variety of signals related to environmental, physiological and emotional stimuli [11], and they innervate much of the brain and spinal cord [12]. Highlighting their key role in regulating arousal, the orexin neurons are reciprocally connected with all brain regions known to promote wakefulness and arousal [13], including the cerebral cortex, basal forebrain (BF), tuberomammillary nucleus (TMN), locus coeruleus (LC), and dorsal raphe (DR) [11,12] (Figure 1). The orexin neurons also innervate brain nuclei that regulate motivation and emotions [14,15], such as the ventral tegmental area (VTA), nucleus accumbens, prefrontal cortex, and amygdala [12]. In addition, the orexin neurons project to many brain regions that regulate motor and autonomic functions [16]. Thus, the orexin system is anatomically well positioned to coordinate many aspects of arousal.

The orexin neuropeptides selectively excite and depolarize target neurons via two distinct G protein-coupled receptors, OX1R and OX2R [7]. OX1R binds orexin-A with higher affinity (~100-fold) than orexin-B, whereas OX2R shows an almost equal affinity for both orexin-A and orexin-B [7,17]. OX1R couples to G_q and OX2R can

Figure 1



Some of the key pathways through which the orexin neurons promote wakefulness. Orexin neurons innervate and excite monoaminergic brain regions such as the locus coeruleus, dorsal raphe, ventral tegmental area, and tubermomammillary nucleus. The orexin neurons also activate cortical neurons directly and indirectly via effects in the basal forebrain.

signal through G_q or G_i/G_o, but coupling mechanisms seem to differ by cell type and have not been thoroughly examined in neurons [17]. The two receptors have partly overlapping but distinct expression patterns in the brain [18]. For example, the LC expresses only OX1R, the TMN produces only OX2R, and many other arousal-promoting brain regions express both receptors (e.g. BF, VTA, DR, and cortex).

The orexin neurons have physiologic properties that may promote sustained activity [for review, see [19]]. The orexin neurons are intrinsically in a depolarized state near their firing threshold, which likely promotes increased spontaneous activity [20]. They also excite other orexin neurons indirectly via local glutamate interneurons and perhaps directly via OX2R on orexin neurons [21,22]. In addition to helping sustain orexin neuron activity, this positive feedback mechanism may also promote recruitment of a larger number of orexin neurons. Furthermore, neighboring astrocytes may influence excitatory inputs to the orexin neurons [23•]. Altogether, these physiologic mechanisms may promote sustained activity in networks of orexin neurons which could then drive persistent activation of a variety of arousal-promoting brain regions.

Orexin neurons and the maintenance of arousal

Orexins are clearly important as they promote arousal and orexin deficiency causes narcolepsy. Central administration of orexin-A produces long wake bouts and increases locomotor activity, while reducing both rapid-eye movement (REM) and non-REM (NREM) sleep [24,25]). Conversely, a mutation in the OX2R gene in dogs or disruption of the prepro-orexin gene in mice causes sleepiness and cataplexy almost identical to that seen in people with narcolepsy [26–28]. In addition, nearly all people with narcolepsy have little or no detectable orexin-A in their cerebrospinal fluid due to extensive loss of the orexin neurons [29]. This topic is reviewed in detail by Dr. Sakurai in this issue.

Mouse models of narcolepsy have provided some of the most helpful information on the mechanisms by which orexin deficiency disrupts arousal. Mutant mice lacking the orexin peptides, orexin neurons, or orexin receptors are unable to sustain long periods of wakefulness and have frequent transitions between sleep/wake states (Figure 2a) [27,28,30–32]. Survival analysis of the durations of wakefulness bouts (Figure 2b) reveals that mice lacking orexins wake normally from sleep but have difficulty producing long-lasting bouts of wakefulness [33] and transition frequently between wakefulness and sleep [34]. Perhaps, in the absence of sustained excitatory signals from the orexin neurons, other arousal-promoting neurons have uncoordinated or inappropriate patterns of activity, resulting in low thresholds for crossing between states and poorly sustained wakefulness. A lack of orexin signaling may also upset the mutually inhibitory balance between sleep-promoting and wake-promoting neurons [35,36•].

Unstable activity in arousal-promoting brain regions may also explain the attentional deficits observed in human narcolepsy [37]. People with narcolepsy have generally normal cognition and show normal phasic arousal during an alertness task that requires their attention for a short period of time [37]. However, they have worsening and increasingly variable performance during tasks lasting more than 10 min, indicating poor maintenance of vigilance. In addition to difficulty sustaining attention over time, patients with narcolepsy also have deficits in divided attention (attention capacity) and flexible attention (attention control). These deficits could be caused by dwindling vigilance due to sleepiness [38], but others have hypothesized they are caused by inappropriate processing of relevant stimuli [39]. Such deficits of selective processing could be a consequence of reduced basal forebrain cholinergic signaling to the cortex [40]. The role of orexins in the BF regulation of attention is discussed later in this review.

Similar to people with narcolepsy, the performance of orexin null mice deteriorates after 10 min of engagement in tasks motivated by food or water reinforcement. Such poor performance results from multiple pauses resembling drowsiness during operant tasks [41•]. Surprisingly, this performance deficit is apparent only during the light