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Antoine Adamantidis, Patrice Fort, Luppi Pierre-Hervé

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The neurophysiology and neurobiology of wakefulness and NREM sleep

Author: Antoine Adamantidis^{1,2}, Patrice Fort^{3,4} and Pierre-Hervé Luppi^{3,4}

Affiliation:

¹ Zentrum für Experimentelle Neurologie, Department of Neurology, Inselspital University Hospital Bern, Bern University, Bern, Switzerland

² Department of Biomedical Research, Inselspital University Hospital Bern, Bern University, Bern, Switzerland

³ Lyon Neuroscience Research Center (CRNL), SLEEP Team; CNRS UMR5292; INSERM, U1028; Lyon, France,

⁴ University Claude Bernard Lyon 1, Lyon, France

Address for correspondence:

Corresponding author : Antoine Adamantidis
University of Bern
Department of Neurology, Inselspital University Hospital Bern,
Freiburgstrasse 18
3011 Bern, Switzerland
Tel number: (+41) 79 288 10 23
E-mail address: antoine.adamantidis@dbmr.unibe.ch

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*Wake and NREM sleep circuits***Abstract**

The present chapter summarizes current hypotheses on the mechanisms underlying the onset, maintenance and termination of waking and non-rapid eye movement (non-REM) also called slow wave sleep. Waking results from the activity of multiple neurotransmitter systems, including the serotonergic, noradrenergic, histaminergic, cholinergic and hypocretin systems. According to the current model, both circadian signals and the progressive accumulation of hypnogenic factors (e.g., adenosine) during waking ultimately activate non-REM-promoting neurons. A number of convincing studies supports the hypothesis that non-REM sleep results from the activation of GABAergic neurons localized at least in the preoptic area of the anterior hypothalamus (POA) leading to the inhibition of the wake-active neurons widely distributed within the whole brain.

Key points

- **The balance between non-REM and waking is due to reciprocal inhibitory projections between non-REM-promoting and wake-promoting neurons widely distributed within the brain.**
- **Amassing experimental studies evidence a multi-circuit origin for NREM sleep.**

Introduction

In mammals, there are three vigilance states characterized by differences in electroencephalogram (EEG), electromyogram (EMG) and electro-oculogram (EOG) recordings. The waking is characterized by high-frequency (40-300 Hz), low-amplitude (desynchronized) EEG activity, sustained EMG activity and ocular movements; non-rapid eye movement sleep (non-REM, also coined slow-wave sleep), is characterized by low-frequency (0.5-4 Hz), high-amplitude (synchronized) EEG oscillations, low EMG activity without ocular movement; and rapid eye movement (REM, also called paradoxical sleep, is defined by a predominant theta (6-9 Hz) and gamma (30-300 Hz) EEG rhythms similar to that of waking concomitant to the disappearance of postural muscle tone and the occurrence of REMs and muscle twitches (Adamantidis, Gutierrez Herrera, & Gent, 2019).

Neuropathological evidence from the 19th century indicates that altered states of vigilance can be induced by focal brain lesions and that different neurochemical mechanisms are responsible for the succession of the vigilance states across the 24 hours day (Fort, Bassetti, & Luppì, 2009). Here we review the experimental evidence demonstrating a role for neuronal networks in the sleep-wake control.

Mechanisms involved in waking

The activated cortical state during waking is induced by the activity of multiple neurochemical systems. Some of these belong to the ascending reticular activating system. Within the brainstem, they include the serotonergic neurons mainly localized in the dorsal raphe nucleus, noradrenergic neurons in the locus coeruleus, cholinergic neurons in the pontine tegmentum. Other rostrally located systems (**Figure 1**) include the cholinergic neurons in the basal forebrain, the histaminergic neurons in the tuberomammillary nucleus, and the hypocretins/orexins system found in the lateral hypothalamus (Fort et al., 2009).

The activation of these systems controls wakefulness and arousal through brain-wide projections in particular those reaching the basal forebrain, thalamus and neocortex, while their descending projections modulate physiological activity (somatosensory and motor systems). It is known for decades that monoaminergic neurons discharge during wakefulness, decrease their activity during non-REM sleep to become silent during REM sleep. The progressive and simultaneous inactivation of all waking systems eventually results in the low-frequency, high-amplitude delta EEG oscillatory activity typical of non-REM sleep and generated by thalamo-cortical networks (Fort et al., 2009). The main brain inhibitory neurotransmitter, the gamma-aminobutyric acid (GABA), likely mediates the sleep-dependant tonic inhibition of the wake-

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active neurons since application of a GABA_A receptor blockers (bicuculline) during non-REM and REM sleep restores their typical wake-related firing in both serotonergic and noradrenergic neurons (Gervasoni et al., 1998; 2000).

Place Figure 1 here

Additional brain areas have been causally implicated in the control of waking. Those include the lateral hypothalamus (LH), a phylogenetically conserved brain region in vertebrates, that is critical for maintaining physiological and behavioural homeostasis, including energy homeostasis, stress response, and goal-oriented behaviours to natural (food, sex) and artificial (drug) rewards. Anatomical and functional evidence indicates that the LH contains a large diversity of cell populations with complex neurochemical profiles (i.e., transmitters, neuropeptides, and multiple transmembrane receptors) and electrophysiological fingerprints. Those include glutamate, GABA, neuropeptide Y (NPY), melanocortins (POMC), substance P, dynorphin, nesfatin-1, Cocaine and Amphetamine-Regulated Transcripts (CART), histamine, Hypocretins/Orexins (Hcrt/Ox), Melanin-Concentrating Hormone (MCH), and dopamine (A11). These neuronal populations form an intricate local and extensive network of excitatory and inhibitory cells, each of which has a specific role in hypothalamic physiological functions.

Solid experimental evidence indicates that neurons located in the LH play also an essential role in the regulation of the sleep-wake states. Electrophysiological recordings of LH cells in freely-moving rodents showed that activity in a wide variety of these neurons correlated with either REM or wake states, and to a lesser extent with non-REM sleep. Amongst those, Hcrt/Ox and MCH neurons showed opposite discharge profiles, with higher activities during waking or REM sleep, respectively (Lee, Hassani, & Jones, 2005; Mileykovskiy, Kiyashchenko, & Siegel, 2005; Takahashi, Lin, & Sakai, 2008). The use of optogenetics have further implicated some these neurons in the onset and maintenance of waking (Adamantidis, Zhang, Aravanis, Deisseroth, & de Lecea, 2007; Carter et al., 2012) and REM sleep (Jego et al., 2013; Konadhode et al., 2013). In addition, LH GABAergic neurons (as defined by their expression of the vesicular glutamic acid transporter, vGAT) showed high discharge rates during either wake (~ 45%), non-REM (<15%), or REM sleep (40%) (Hassani, Henny, Lee, & Jones, 2010), indicating a strong heterogeneity amongst hypothalamic GABA cells. Beside local GABA inter-neurons, a large proportion of wake-promoting GABA neurons with LH send long-range ascending projections to sleep nuclei in the POA, where they inhibit sleep-promoting neurons

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(Venner, Anaclet, Broadhurst, Saper, & Fuller, 2016), as well as in the thalamus and cerebral cortex. Interestingly, some of these neurons synapse onto thalamic reticular (RTN) neurons and induce arousal exclusively from non-REM (Herrera et al., 2016) through a feedforward disinhibition of thalamo-cortical networks, and to a lesser extent to arousal-promoting LC. These studies demonstrate a large functional diversity among inhibitory LH neuron populations implicated in waking control, which remains to be fully elucidated.

Finally, recent works identified new populations of neurons whose opto- or chemogenetic activation results in rapid transition from sleep to waking. Those include dopaminergic neurons from the ventral tegmental area (VTA) (Eban-Rothschild, Rothschild, Giardino, Jones, & de Lecea, 2016), neurons located in the supramammillary nuclei (Pedersen et al., 2017), the external lateral parabrachial nucleus (Kaur et al., 2017, Qiu, Chen, Fuller, & Lu, 2016), or the pedunculopontine tegmental (PPT) nucleus (Kroeger et al., 2017), dopamine D1 receptor (D1R)-expressing neurons in the nucleus accumbens (Luo et al., 2018) and GABAergic neurons from the superior colliculus (Z. Zhang, Liu, et al., 2019a). Neural circuits supporting the onset and maintenance of wakefulness show a high redundancy, however, whether these circuits support redundant or specific/selective regulatory pathways remains to be investigated.

Mechanisms involved in the onset and maintenance of non-REM sleep

Our understanding of the neural mechanisms underlying non-REM sleep have progressed over the last decades, yet its brain-wide organization in space and time remains unclear. Recent studies identified multiple cell population whose activity strongly correlates with NREM sleep in several brain areas, suggesting a multiple origin of NREM sleep onset.

Original study from the neuropathologist von Economo followed patients with post-influenza encephalitis and reported that inflammatory lesions of the preoptic area (POA) within the anterior hypothalamus were often associated with insomnia and therefore proposed that the POA was critical for the production of normal sleep (Economo C, 1930). This was further confirmed in monkeys, rats, and cats where POA lesions or stimulation consistently induced a profound and persistent insomnia, or EEG slow wave activity and non-REM sleep respectively (Fort et al., 2009). Consistent with this findings, putative sleep-promoting neurons displaying an elevated discharge rate that positively correlate with sleep depth and non-REM sleep duration, as compared to waking were recorded in within a large region encompassing the horizontal limb of the diagonal bands of Broca, POA and substantia innominata in freely-

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moving cats (Fort et al., 2009). Some of these neurons are also active during PS with a higher firing frequency than during the preceding non-REM sleep. Interestingly, the number of c-Fos-immunoreactive neurons in the ventrolateral (VLPO) and median (MnPn) preoptic nuclei of the POA positively correlated with sleep quantity and sleep consolidation, suggesting that VLPO neurons are responsible for the induction of sleep while MnPn neurons serve a homeostatic role in sleep (Gvilia, Xu, McGinty, & Szymusiak, 2006; Sherin, Elmquist, Torrealba, & Saper, 1998). It was later demonstrated that VLPO and the suprachiasmatic nucleus (SCN), responsible for the circadian organization of the sleep-waking cycle, have synchronized activity. Considering that both areas are interconnected and receive inputs from the retinal ganglion cells, it is, thus, possible that circadian- and photic-linked information may be conveyed to modulate VLPO activity (Fort et al., 2009) (**Figure 2**). Retrograde and anterograde tract-tracing studies indicate that VLPO and MnPn neurons are synaptically connected with, and fire in a reciprocal pattern (i.e. opposite) than, the wake-active neurons (see below). In these wake-promoting areas, extracellular levels of GABA, of putative hypothalamic origin, increase during SWS compared to waking, as suggested by GABA-mediated inhibition of TMN neurons upon electrical stimulation of the VLPO area (Fort et al., 2009). Accordingly, a recent study further characterized the chemical nature sleep-promoting inhibitory neurons in this area that were originally described found to express both galanin and glutamic acid decarboxylase (GAD), the GABA-synthesizing enzyme (Chung et al., 2017). Furthermore, Chemogenetic activation of VLPO galanergic neurons induced an increase in NREM sleep, accompanied with a decrease of REM sleep duration and body temperature in mice (Kroeger et al., 2018). This sleep-temperature response belongs to the physiological changes in brain and the body that occur at sleep onset, and question the role of VLPO neurons as the unique substrate for NREM sleep in the mammalian brain (see below).

Electrophysiological whole-cell recordings showed that VLPO contains neuronal groups with specific intrinsic membrane properties, distinct chemo-morphology and that they are inhibited by most of the waking neurotransmitters (Gallopín et al., 2000; 2005). Sleep-active neurons are GABAergic and galanergic in nature, multipolar triangular shaped, and exhibit a potent low threshold calcium potential. These neurons are always inhibited by noradrenaline (NA), via postsynaptic alpha2-adrenoceptors. Interestingly, NA-inhibited neurons are also inhibited by acetylcholine, through muscarinic postsynaptic and nicotinic presynaptic actions on noradrenergic terminals. In contrast, histamine and hypocretin did not modulate the activity of the sleep-active neurons. Finally, serotonin induced either excitation (50%, Type 2) or inhibition (50%, Type 1) of VLPO neurons (Gallopín et al., 2005; Sangare, Dubourget,

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Geoffroy, Gallopin, & Rancillac, 2016). Recent studies indicate that glucose is able to promote sleep by activating VLPO neurons (Varin et al., 2015), possibly through astrocyte-release adenosine (Scharbarg et al., 2016)

Early sleep-wake models (Saper, Fuller, Pedersen, Lu, & Scammell, 2010) posit that sleep onset result from a sustained coordinated inhibition of the multiple arousal systems of the ascending reticular activating system (ARAS) by the hypnogenic center, namely POA-based circuits (**Figure 2**). Conversely, emergence from sleep would results from a rapid reactivation of arousal circuits, concomitant with the inhibition of VLPO neurons (Fort et al., 2009). However, this remains to be demonstrated in light of the complexity of the network responsible for sleep-wake states. Indeed, over the last years, several populations of neurons disseminated from the upper brainstem, to the hypothalamus and basal forebrain.

Place Figure 2 here

Sleep is homeostatically regulated because sleep pressure progressively builds up during waking and dissipate during sleep (Fort et al., 2009; Saper et al., 2010). Therefore, natural sleep-promoting factors accumulating during waking represent homeostatic regulators that are essential to the triggering of sleep. Yet, the underlying mechanisms remains unclear. Among these factors, prostaglandin D2 and adenosine have been functionally implicated in sleep, although their neuronal targets and mechanisms of action remain largely unknown. Indeed, application of an adenosine, or an A_{2A} receptor ($A_{2A}R$) agonist, evoked direct excitatory effects on sleep-active neurons (Fort et al., 2009), induces c-Fos expression in VLPO neurons and increases SWS in rodents (Lazarus, Huang, Lu, Urade, & Chen, 2012) (**Figure 2**). Interestingly, some of the adenosine effects show site-specific modulatory action. Inhibition of the expression of $A_{2A}R$ in the shell region of the nucleus accumbens (NAc) is sufficient to block the induction of waking induced by caffeine (Lazarus et al., 2012). This finding suggests that the induction of sleep not only results from the activation of VLPO neurons, but also from the adenosine activation of $A_{2A}R$ and inhibition of NAc GABAergic neurons (Lazarus et al., 2012). Supporting this view, adenosine A_1 receptors (A_1R) promote sleep through inhibition of the wake-promoting neurons, in particular cholinergic and hypocretins/orexins neurons

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(Porkka-Heiskanen, Strecker, & McCarley, 2000), despite the finding that transgenic mice that lack A₁R exhibit normal homeostatic regulation of sleep. In contrast, the lack of A_{2A}R prevents normal sleep regulation and blocks the wake-inducing effect of caffeine, suggesting that the activation of A_{2A}R is crucial in SWS (Huang, Urade, & Hayaishi, 2011).

Over the last years novel technologies such as opto-, or chemo-, genetic approaches to manipulate the activity of genetically targeted neurons were essential in identifying a substantial number of neurons whose activity, or lack thereof, is causally involved with the onset, or maintenance, of NREM sleep. Interestingly what was previously identified as inhibitory cells from the POA was dissected in several sub-population of neurons all promoting NREM sleep (Chung et al., 2017). In addition, neurons from the nucleus accumbens (A_{2A}R) (Oishi et al., 2017), GABAergic neurons from the parafacial zone (Anaclet et al., 2014; Anaclet, Griffith, & Fuller, 2018), neurotensinergic from the midbrain (Zhong et al., 2019) and GABAergic of the ventral medial midbrain/pons (Takata et al., 2018), as well as some excitatory neurons from the perioloculomotor nuclei (Z. Zhang, Zhong, et al., 2019b), POA-projecting galanin-expressing GABAergic neurons in the dorsomedial hypothalamus (DMH) (K.-S. Chen et al., 2018), somatostatin-positive (SOM+) GABAergic neurons (M. Xu et al., 2015), neurons from the midbrain RMTg nuclei (Yang et al., 2018), as well as striatal A_{2A}R neuron /GPe PV neuron circuits involved in the adenosine-induced sleep (Yuan et al., 2017), all were found to induce NREM sleep with variable latencies.

Finally, NREM sleep is defined primarily by a specific set of cortical EEG oscillations including slow waves, delta waves or sleep spindles all of which results from thalamo-cortical circuit activity (Adamantidis et al., 2019). Thus, neurons located in the neocortex and thalamus have been suggested to play a role in NREM sleep regulation. As such, cortical interneurons expressing neuronal nitric oxide synthase (nNOS) control both NREM amount and slow wave activity (Gerashchenko et al., 2008). Similarly, patterned activity of somatostatin and parvalbumin neurons underlies NREM sleep slow wave generation and propagation (Beltramo et al., 2013; Funk et al., 2017; Neske & Connors, 2016). At the cellular level, some of these rhythms in the frontal area of the brain are under a direct modulation by neurons of the medio-dorsal thalamus (Gent, Bandarabadi, Herrera, & Adamantidis, 2018a; Lemieux, Chauvette, & Timofeev, 2015). At the behavioural level, tonic firing of medio-dorsal thalamic neurons is associated with the onset and maintenance of waking, while their burst firing is associated with a sleep-promoting function (Gent et al., 2018a; Giber et al., 2015). These findings suggest that

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these neurons, and probably unidentified others, represent a functional hub that integrates converging subcortical inputs into synchronous thalamo-cortical network activities typical of NREM sleep (Gent, Bassetti, & Adamantidis, 2018b). How are these oscillatory activities orchestrated in space and time, together with the typical cellular activity found in the anterior hypothalamus, basal forebrain, midbrain and lower brainstem (described above), across the different vigilance states remains to be investigated.

Conclusion

Since the first identification of sleep-promoting neurons in the preoptic and anterior hypothalamus (Fort et al., 2009; Saper et al., 2010), the use of new technologies to either correlate (e.g., single unit recording, cell activity imaging) neuronal activities with sleep-wake states have led to the identification of multiple circuits involved in NREM sleep. Some of these were further confirmed to be critically involved in some aspect of NREM sleep using pharmaco- and opto-genetics in rodents. Yet, the precise mechanisms underlying the onset and homeostatic control of NREM sleep remain unclear. In addition to the POA/VLPO/MnPn nuclei originally implicated in the mechanisms of waking/NREM sleep alternation (flip-flop model), we reviewed an amassing number of novel neural circuits likely contributing to the control of NREM sleep that is consistent with the global-to-local paradigm shift of sleep control. Collectively these studies all support a multiple origin of NREM sleep, that strikingly resemble the functional architecture of the numerous wake-promoting circuits of the mammalian brain. Whether they represent redundant or highly specialized circuitries remains to be investigated.

Figure legend**Figure 1.** Neuronal networks responsible for waking.

At sleep-wake transitions, the hypocretin neurons would be the first to start firing, exciting all the other waking systems (histaminergic, monoaminergic and cholinergic). In turn, these waking systems activate the thalamus and/or the cortex, leading to cortical activation and also, importantly, inhibit the GABAergic SWS (Non-REM sleep)-active neurons of the VLPO and MnPn.

Abbreviations: 5HT, 5-hydroxytryptamine (serotonin), Ach, acetylcholine; ADA, adenosine; BF, basal forebrain; DPGi, dorsal paragigantocellular reticular nucleus; dDPMe, deep mesencephalic reticular nucleus; DRN, dorsal raphe nucleus; GABA, gamma-aminobutyric acid; GiV, ventral gigantocellular reticular nucleus; Gly, glycine; Hcrt, hypocretin (orexin)-containing neurons; His, histamine; LC, locus coeruleus; LdT, laterodorsal tegmental nucleus; MCH, melanin concentrating hormone-containing neurons; NA, noradrenaline; PH, posterior hypothalamus; PPT, pedunclopontine tegmental nucleus; PS, paradoxical sleep; RT, reticular thalamic neurons; SCN, suprachiasmatic nucleus; SLD, sublaterodorsal nucleus; SWS, slow-wave sleep; TMN, tuberomamillary nucleus; vLPAG, ventrolateral periaqueductal gray; VLPO, ventrolateral preoptic nucleus; W, waking.

Figure 2. Neuronal networks responsible for slow-wave (non-rapid-eye movement [REM]) sleep.

VLPO and MnPo GABAergic neurons would be inhibited by noradrenergic and cholinergic inputs during waking. The majority of them would start firing at sleep onset (drowsiness) in response to excitatory, homeostatic (adenosine) and circadian drives (suprachiasmatic input). These activated neurons, through the reciprocal GABAergic inhibition of all wake-promoting systems, would be in a position to suddenly unbalance the “flip-flop” network, as required for

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switching from waking (drowsiness) to a consolidation of SWS sleep. Conversely, the slow removal of excitatory influences would result in a progressive firing decrease in VLPO neurons and therefore an activation of wake-promoting systems leading to the awakening event.

For Review Only

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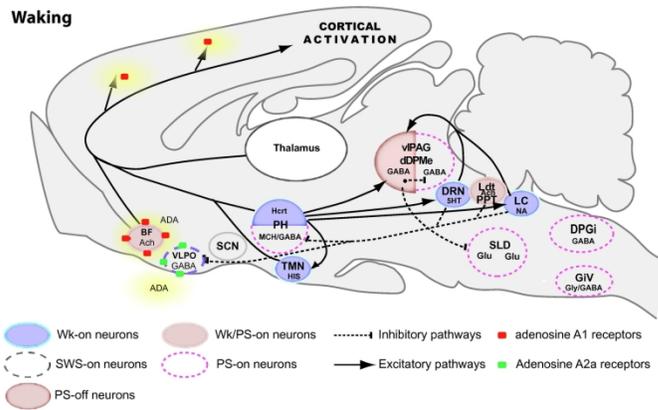


Figure 1. Neuronal networks responsible for waking.

At sleep-wake transitions, the hypocretin neurons would be the first to start firing, exciting all the other waking systems (histaminergic, monoaminergic and cholinergic). In turn, these waking systems activate the thalamus and/or the cortex, leading to cortical activation and also, importantly, inhibit the GABAergic SWS (Non-REM sleep)-active neurons of the VLPO and MnPn.

Abbreviations: 5HT, 5-hydroxytryptamine (serotonin), Ach, acetylcholine; ADA, adenosine; BF, basal forebrain; DPGi, dorsal paragigantocellular reticular nucleus; dDPMe, deep mesencephalic reticular nucleus; DRN, dorsal raphe nucleus; GABA, gamma-aminobutyric acid; GiV, ventral gigantocellular reticular nucleus; Gly, glycine; Hcrt, hypocretin (orexin)-containing neurons; His, histamine; LC, locus coeruleus; Ldt, laterodorsal tegmental nucleus; MCH, melanin concentrating hormone-containing neurons; NA, noradrenaline; PH, posterior hypothalamus; PPT, pedunculopontine tegmental nucleus; PS, paradoxical sleep; RT, reticular thalamic neurons; SCN, suprachiasmatic nucleus; SLD, sublaterodorsal nucleus; SWS, slow-wave sleep; TMN, tuberomammillary nucleus; vIPAG, ventrolateral periaqueductal gray; VLPO, ventrolateral preoptic nucleus; W, waking.

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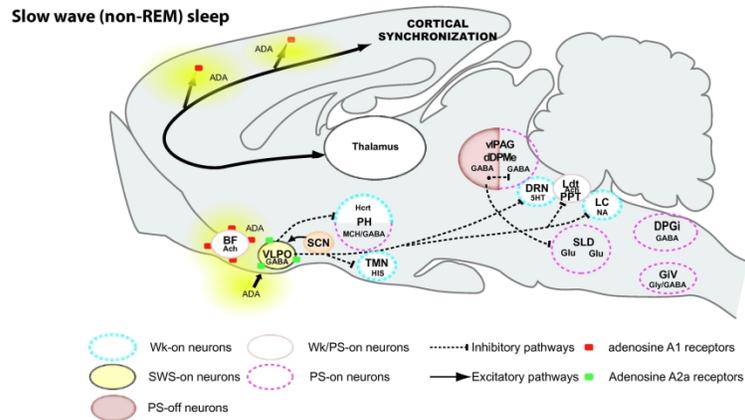


Figure 2. Neuronal networks responsible for slow-wave (non-rapid-eye movement [REM]) sleep. VLPO and MnPo GABAergic neurons would be inhibited by noradrenergic and cholinergic inputs during waking. The majority of them would start firing at sleep onset (drowsiness) in response to excitatory, homeostatic (adenosine) and circadian drives (suprachiasmatic input). These activated neurons, through the reciprocal GABAergic inhibition of all wake-promoting systems, would be in a position to suddenly unbalance the “flip-flop” network, as required for switching from waking (drowsiness) to a consolidation of SWS sleep. Conversely, the slow removal of excitatory influences would result in a progressive firing decrease in VLPO neurons and therefore an activation of wake-promoting systems leading to the awakening event.