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The menagerie of the basal forebrain: How many (neural) species are there, what do they look like, how do they behave and who talks to whom?

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Abstract

The diverse cell-types of the basal forebrain control sleep-wake states, cortical activity and reward processing. Large, slow-firing, cholinergic neurons suppress cortical delta activity and promote cortical plasticity in response to reinforcers. Large, fast-firing, cortically-projecting GABAergic neurons promote wakefulness and fast cortical activity. In particular, parvalbumin/GABAergic neurons promote neocortical gamma band activity. Conversely, excitation of slower-firing somatostatin/GABAergic neurons promotes sleep through inhibition of cortically-projecting neurons. Activation of glutamatergic neurons promotes wakefulness, likely by exciting other cortically-projecting neurons. Similarly, cholinergic neurons indirectly promote wakefulness by excitation of wake-promoting, cortically-projecting GABAergic neurons and/or inhibition of sleep-promoting somatostatin/GABAergic neurons. Both glia and neurons increase the levels of adenosine during prolonged wakefulness. Adenosine presynaptically inhibits glutamatergic inputs to wake-promoting cholinergic and GABAergic/parvalbumin neurons, promoting sleep.

INTRODUCTION

The basal forebrain (BF) is a large heterogeneous structure located close to the ventral surface of the rostral telencephalon (Figure 1) which is involved in sleep-wake control, attention and reward processing [1–3]. Until relatively recently, most of these functions were ascribed to the BF cholinergic neurons which degenerate in Alzheimer's disease and other dementias [4]. However, recent technical advances which allowed the specific targeting of GABAergic and glutamatergic BF neurons have revealed important roles for these neurons and have refined our understanding of cholinergic neurons [2]. Thus, in this review we summarize our current knowledge of these different neural species within the BF menagerie. We discuss their cellular properties (what they look like), their functions (how they behave)

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and how they interact (who talks to whom). We focus on the intermediate/caudal part of BF which contains neurons projecting to the neocortex (Figure 1) and on studies conducted in mice, since recent optogenetic and chemogenetic studies have used this species.

HOW MANY NEURAL SPECIES ARE THERE AND WHAT DO THEY LOOK LIKE?

The BF contains three largely non-overlapping groups of neurons [5–8] which can be distinguished based on their neurotransmitter phenotype i.e. cholinergic, GABAergic and glutamatergic neurons. GABAergic and glutamatergic neurons can be further subdivided according to their projections, their expression of calcium-binding proteins, neuropeptides/ neuropeptide receptors, ion channels and their intrinsic electrical properties, as described next. Figure 2 gives an overview.

Properties and subtypes of cholinergic neurons

Cholinergic neurons are typically identified by their expression of choline acetyltransferase [9], the enzyme which synthesizes acetylcholine. Although they are the best known of the different BF neuronal species, cholinergic neurons represent a minority of BF neurons (10–20%, depending on the subregion) [8]. Cholinergic neurons are mostly large neurons (>20 μm), and are present throughout all BF subregions [6,10]. Most BF cholinergic neurons express the low-affinity neurotrophin receptor, p75 [8], and densely innervate the entire cortical mantle in a selective and topographically specific manner [8,11–14]. A smaller subset of cholinergic neurons lacks the p75 receptor and projects to the amygdala [8,15,16]. Some of these neurons also express the vesicular glutamate transporter, subtype 3 [15]. BF cholinergic neurons receive dense inputs from subcortical nuclei related to motivation and stress such as the amygdala, lateral hypothalamus and dorsal raphe [17].

In vitro, BF cholinergic neurons are often silent at rest (resting membrane potential ~−70 mV), discharge slowly with large and long-lasting afterhyperpolarizations when depolarized, and have a low tonic maximal firing rate of ~14 Hz [6], although higher rates are observed within burst discharges *in vivo* [18]. BF cholinergic neurons are excited by most wake-promoting neurotransmitters, but are inhibited by serotonin [1].

Properties and subtypes of GABAergic neurons

BF GABAergic neurons represent the largest group of BF neurons. Stereological estimates in rats suggest there are ~5 times more GABAergic than cholinergic neurons [19]. The recent availability of transgenic mouse models, such as the glutamic acid decarboxylase 67 (GAD67)-GFP knock-in and vesicular-GABA-transporter (vGAT)-Cre Recombinase mice, has helped overcome previous technical challenges in targeting them, and allowed the precise mapping and determination of their properties [5–7]. Most are small or medium-sized (<20 μm) neurons but ~12% are large sized (>20 μm) projection neurons [6,20]. The densest cluster of large-sized BF GABAergic neurons in the mouse is located laterally in the magnocellular preoptic nucleus [6]. Cortical projections of BF GABAergic neurons preferentially target cortical interneurons containing parvalbumin or somatostatin [21,22]. Other prominent BF GABAergic outputs target the thalamic reticular nucleus [5,23], midline

thalamus [5], lateral hypothalamus [24] and lateral habenula [5,11,25]. A recent study identified a GABAergic BF projection to the lateral habenula which modulates aggression reward [25].

In vitro, large BF GABAergic neurons have a high spontaneous (~13 Hz) and maximal discharge rate (90 Hz or higher). Based on the amplitudes and kinetics of their hyperpolarization-activated cationic current (I_h), these large-sized BF GABAergic neurons can be further categorized into two subtypes, large I_h and small I_h [6]. Both subtypes exhibit electrical synapses linking neighboring neurons [6], which may be important for synchronizing their firing [26].

At least three types of large, cortically-projecting BF GABAergic neurons exist [27]. One functionally important subgroup (~25 % of large GABAergic neurons and ~7 % of all GABAergic neurons) [6], involved in the control of cortical gamma band oscillations [22], contains the calcium binding protein, parvalbumin (PV) [6,20]. They have very narrow action potentials and extremely high maximal discharge rates, like cortical PV interneurons [6]. Unlike cortical PV interneurons however, they exhibit prominent H-currents, a depolarized membrane potential and different pharmacology [2,6,27]. A second, large population (60 %) of BF GABAergic neurons located in HDB and MCPO expresses a particular type of delayed rectifier potassium channels (Kv2.2) [28]. Neurokinin B receptors (NK3Rs), which are involved in secretion of gonadotropin-releasing hormone, are expressed in a largely separate population (~25%) of BF cortically-projecting GABAergic neurons [29].

Many BF GABAergic neurons project caudally and/or locally within BF. Some of these smaller GABAergic neurons have intrinsic electrical properties similar to striatal medium-spiny neurons [6]. Subsets of BF GABAergic neurons co-express the neuropeptides somatostatin or neuropeptide Y, the enzyme nitric oxide synthase or the calcium binding proteins, calbindin or calretinin [8,20].

Properties and subtypes of glutamatergic neurons

Glutamatergic neurons represent the smallest of the three major groups of BF neurons. Most contain the vesicular glutamate transporter, subtype 2 (vGluT2) [8,30], with much smaller numbers expressing vGluT1 (Allen Brain Atlas) or vGluT3 [15]. The vast majority of BF vGluT3 neurons are cholinergic [15]. vGluT2 neurons comprise ~5% of BF cortically-projecting neurons [30]. Tracing experiments [11,30] suggest that vGluT2 neurons have relatively weak projections to cortex but stronger projections to many subcortical regions, including areas involved in reward processing such as the lateral habenula, as well as within the BF [7]. Cortically-projecting vGluT2 neurons are located mainly in ventromedial BF [30]. Like BF GABAergic neurons, subsets of BF glutamatergic neurons express calcium binding proteins [20]. In the rat, it was proposed that calbindin-expressing glutamatergic neurons project to cortex while calretinin-containing neurons project locally or caudally [5,20]. A subgroup (25%) of vGluT2 neurons in rostral BF express gonadotropin-releasing hormone [31]. In vitro, BF vGluT2 neurons discharge maximally around 50 Hz (Yang et al., abstract in *SLEEP Abstract Supplement* 2016, 39:0075). Most vGluT2 neurons exhibit

moderately-sized Ih although there is subregional variability. Subsets of vGluT2 neurons have low-threshold calcium currents and show burst/cluster discharge.

HOW DO THEY BEHAVE?

In vivo discharge and role of different BF neurons in the control of sleep-wake activity, attention and reward

Behavior of BF cholinergic neurons—BF cholinergic neurons are more active during wakefulness and rapid-eye-movement (REM) sleep than during non-REM (NREM) sleep [7,18]. Furthermore, they discharge with bursts of action potentials during states associated with EEG theta activity. Behavioral studies revealed a rapid response to reinforcers [32,33]. Cholinergic signals in the cortex promote cortical activation [34], facilitate fast and dynamic plasticity of sensory perception [35], enhance the salience of stimuli [36] and promote long-lasting synaptic plasticity [37]. Thus, one main function of cholinergic neurons may be to act as a teaching and alerting signal to the cortex in the presence of behaviorally important stimuli. Caudal projections of BF cholinergic neurons whose cell bodies are located in the diagonal band are also reward-related since they modulate appetite [38].

Recent optogenetic and chemogenetic studies tested the role of BF cholinergic neurons in the promotion of wakefulness. Phasic optogenetic activation of BF cholinergic neurons increased transitions to wakefulness [39,40] or the amount of wakefulness during the period of stimulation [41], enhanced cortical theta activity [7,39–41] and suppressed delta activity [42,43]. However, short-term, wake-promoting effects were dependent on activation of neighboring BF neurons [41]. Prolonged chemogenetic activation of cholinergic neurons also reduced delta activity and increased the number of wake bouts but did not change the total amount of wakefulness [5]. Selective lesion or chemogenetic inhibition studies showed only mild changes in sleep-wake amounts [42–45]. Together, these results support the opinion that the BF cholinergic system itself has a relatively minor direct role in controlling the overall daily amounts of wakefulness but, similar to other neuromodulatory systems, enhanced activity of cholinergic neurons can temporally increase wakefulness in certain behavioral contexts.

In contrast to its relatively minor role in controlling spontaneous sleep/wake behavior, considerable work supports a key role of the BF cholinergic system in the homeostatic sleep response. Specific lesions of cholinergic neurons expressing the p75 neurotrophin receptor abolished increases in sleep and EEG delta power following sleep deprivation [44,46]. In addition, increases in the inhibitory neuromodulator, adenosine [47,48], during prolonged wakefulness [49] were blocked by cholinergic lesions [46].

Behavior of BF GABAergic neurons—Unlike the relatively homogeneous cholinergic neurons, the discharge of identified BF GABAergic neurons shows considerable diversity [50]. One third of BF GABAergic neurons which show state-dependent modulation, likely the cortically-projecting GABAergic neurons, discharge maximally during wakefulness and REM sleep and in positive correlation with gamma EEG activity [50]. Identified PV neurons also show this pattern of activity [7,22,51]. Interestingly, single-unit recordings by Hangya and colleagues suggested that the discharge of a non-cholinergic BF neuronal population

with discharge rates similar to identified wake/REM-active GABAergic or PV neurons were correlated with attention [32]. Another third of GABAergic neurons discharged maximally during NREM sleep and in positive correlation with EEG delta activity. At least some of these GABAergic neurons contain somatostatin [7] or NPY [51]. The final third discharge maximally during REM sleep and in negative association with electromyographic (EMG) activity [50]. Additional markers to identify this subgroup of GABAergic neurons are lacking at present. A subpopulation of slowly-discharging, non-cholinergic BF neurons, possibly GABAergic, which lack strong state-dependent modulation of discharge encode motivational salience [2,52].

Chemogenetic activation of BF GABAergic neurons in vesicular GABA transporter-Cre Recombinase (vGAT-cre) mice strongly increased total amounts of wakefulness and high-frequency cortical rhythms (>30 Hz) [5,7,22] whereas chemogenetic inhibition increased the percentage of time spent asleep [5], suggesting an essential role for a major subset of BF GABAergic neurons in promoting wakefulness. However, the role of specific subtypes of BF GABAergic neurons is still an active area of investigation. Optogenetic stimulation of BF PV neurons preferentially enhanced cortical gamma oscillations (~40 Hz) [22] likely by synchronizing cortical PV interneurons [21]. This effect was independent of BF cholinergic neurons. Furthermore, bilateral optogenetic inhibition of BF PV neurons impaired the 40 Hz auditory steady-state cortical response [22]. Optogenetic stimulation of PV neurons induces short-latency arousals from sleep (McKenna, Thankachan et al., abstract in *Soc. Neurosci Abs 2016, 83.10)* and increased total amounts of wakefulness [7]. However, loss-of-function experiments with respect to sleep-wake behavior have not been performed to date. C-fos immunostaining suggests that BF Kv2.2-expressing GABAergic neurons are also likely to be wake-active neurons [53]. Furthermore, global knockout of Kv2.2 reduced cortical delta power during sleep [53]. To date, single-unit recordings from cortically-projecting Kv2.2/GABAergic or NK3R/GABAergic neurons have not been performed.

Somatostatin/GABAergic neurons are heterogeneous with respect to their discharge pattern. Some are wake/REM active whereas others discharge faster during NREM sleep [7]. Despite only a portion of BF Somatostatin neurons being more active during NREM sleep, optogenetic stimulation of these neurons increased NREM sleep and decreased wakefulness [7].

Behavior of BF glutamatergic neurons—The discharge of BF vGluT2 neurons is weakly modulated across brain states. They are primarily wake and REM active [7]. Strong optogenetic stimulation of BF vGluT2 neurons potently promotes wakefulness [7], however weaker chemogenetic activation of BF vGluT2 neurons only decreased NREM delta power without affecting sleep-wake quantity, consolidation or sleep latency [5]. Loss-of-function studies of BF vGluT2 neurons have not been performed to date so it is unclear whether they are *necessary* for sleep-wake control. Recordings of calcium signals from vGluT2 neurons *in vivo* revealed that they, like other BF cell-types, are activated by punishers [33]. Rostral vGluT2 neurons control hippocampal theta oscillations and locomotion [54,55].

Basal forebrain glial cells—Very little is known about the types and physiology of glia in BF. Microglia play an important role in the differentiation, development and survival of

BF cholinergic neurons [56]. Importantly for sleep-wake control, astrocytes contribute to sleep-deprivation induced increases in extracellular adenosine, through release of ATP [57]. ATP released as a co-transmitter and adenosine released from neurons via adenosine transporters are also important contributors to sleep deprivation-induced increases in extracellular adenosine [58].

WHO TALKS TO WHOM? THE BF LOCAL CELLULAR NETWORK

Understanding the interactions of different BF neuronal species (Figure 3) is key to the interpretation of studies which investigate the role of specific subsets of BF neurons in behavior. For instance, recent experiments revealed a strong excitatory effect of cholinergic neurons on cortically-projecting GABAergic neurons mediated by nicotinic and muscarinic M1/M3 receptors [7,10], whereas the most prominent effect on vGluT2 neurons is a strong, long-lasting inhibition [7]. *In vivo* optodialysis experiments revealed that these local interactions, most likely the excitation of GABAergic neurons, were necessary for stimulation of cholinergic neurons to induce wakefulness [41].

In contrast to the extensive local effects of cholinergic neurons, BF PV/GABAergic neurons have relatively sparse connections to other BF neurons [7] suggesting that BF GABAergic [5] or PV neurons [22] promote wakefulness via their direct cortical projections, although interactions with other subcortical nodes of the sleep-wake circuitry [11] cannot be ruled out. The connections of Kv2.2 and NK3R GABAergic neurons are unknown at present.

Somatostatin/GABAergic neurons inhibit BF cholinergic, PV and vGluT2 neurons [7]. Thus, it is perhaps not surprising that optical stimulation of these neurons promoted sleep [7]. While the enhanced NREM discharge of a subset of these neurons would be consistent with a role in sleep promotion, loss-of-function experiments will be necessary to establish if they are necessary.

vGluT2 neurons provide excitatory inputs to all other BF neuronal subtypes [7]. Thus, the wake-promoting effects of stimulation of these neurons may be due to local interactions [7] or due to their extra-BF projections [11,30]. Loss-of-function experiments for this neuronal group have not been reported.

CONCLUSIONS

Overall, the current evidence is strongest with regards to an essential role for cortically-projecting GABAergic neurons in promoting wakefulness and cortical fast activity (Figure 3). Cholinergic neurons can increase wakefulness through their intra-BF and cortical projections and are important for cortical processing and plasticity in response to rewards and punishers. In addition, they play a key role in sleep homeostasis. The functional role of glutamatergic neurons is largely unexplored but at a minimum they act as local interneurons providing excitatory input to other BF cell-types. In the future, it will be important to dissect out the role of distinct subtypes of cholinergic, GABAergic and glutamatergic BF neurons and their postsynaptic targets.

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Highlights

- Cholinergic, GABA and glutamatergic neurons all affect cortical activation
- Cholinergic neurons suppress cortical delta activity and promote cortical plasticity
- GABA/parvalbumin neurons promote gamma activity and fast arousals from sleep
- GABA/somatostatin neurons inhibit wake-promoting neurons
- Increases in extracellular adenosine promote sleep during prolonged wakefulness

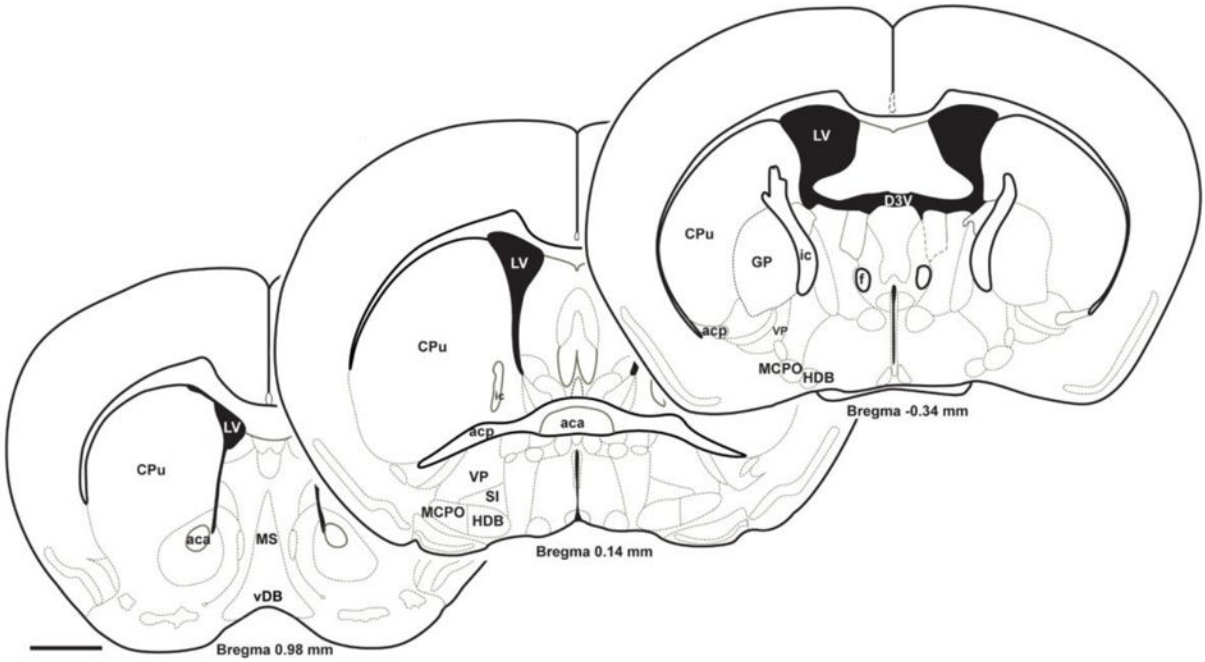

Figure 1.

The basal forebrain (BF) is a large, heterogeneous structure located adjacent to the ventral surface of the forebrain. It is typically defined by the presence of cholinergic projection neurons [8] although as we discuss here, GABAergic and glutamatergic neurons play important functional roles. Rostral BF regions (MS, vDB) contain neurons which project to the hippocampus and associated archaecortical regions. This review is mainly focused on intermediate BF subregions with neurons projecting to neocortex, including MCPO, HDB, VP and SI as well as caudally-located cholinergic and GABAergic projection neurons in the nucleus basalis (a term often used interchangeably with basal forebrain in the human literature) located within the boundaries of the globus pallidus (GP). This figure was adapted with permission from figures previously published in “The mouse brain in stereotaxic coordinates” (ISBN: 9780123910578) by George Paxinos & Keith Franklin (2008) 3rd ed. New York, Academic Press (Copyright Elsevier). *Abbreviations*: aca: anterior part of anterior commissure; acp: posterior part of anterior commissure; CPu: caudate putamen; D3V: dorsal 3rd ventricle; f: fornix; GP: globus pallidus; HDB: horizontal limb of the diagonal band; ic: internal capsule; LV: lateral ventricle; MCPO: magnocellular preoptic nucleus; MS: medial septum; SI: substantia innominata; vDB: ventral limb of the diagonal band; VP: ventral pallidum. Scale bar=1mm.

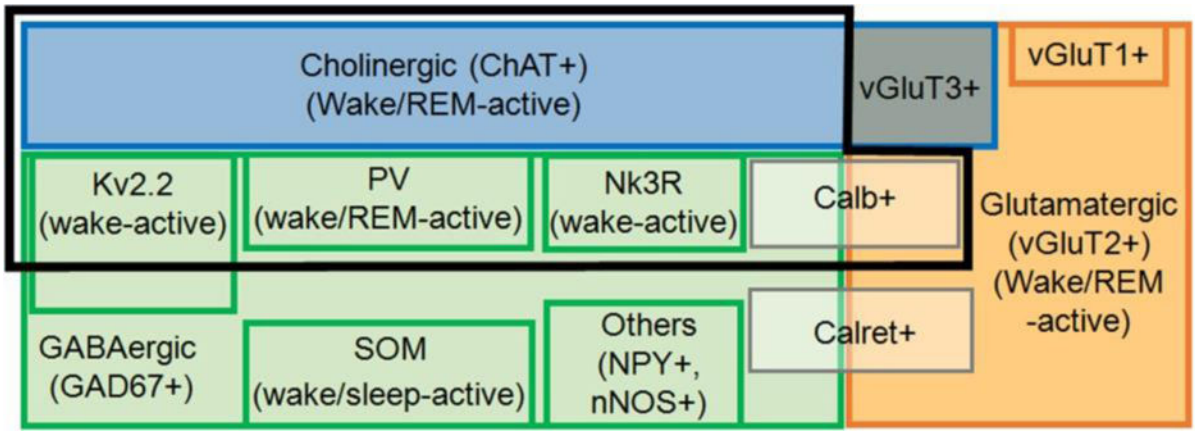

Figure 2. Basal forebrain neuronal subtypes and their discharge properties across sleep-wake states

Blue represents the well-known cholinergic (ChAT+) population representing ~10–20 % of all BF neurons, depending on the subregion [8]. Green represents the GABAergic (GAD67+) population, the largest group of BF neurons, ~5 times the number of cholinergic neurons [19]. Orange represents the smaller glutamatergic population (mainly vGluT2+ with small numbers of vGluT1+ and vGluT3+ neurons; [30]). A few vGluT3 neurons are cholinergic (grey/blue box) and project to the amygdala [15]. The black frame represents cortically-projecting neuronal subtypes, including most cholinergic neurons, three different types of GABAergic neurons and glutamatergic (vGluT2) neurons. Cortically-projecting neurons are active during wakefulness and/or REM-sleep in association with cortical fast-activity [7,18,50,51]. GABAergic PV neurons are wake/REM active [7,22]. They represent ~7 % of all BF GABA neurons but ~25 % of large (>20 μm, likely cortically-projecting neurons) [6]. GABAergic Kv2.2+ neurons represent ~60 % of all BF GABAergic neurons in HDB and MCPO [28], including large putative cortically-projecting neurons. Nk3R+ neurons represent a third group of cortically-projecting GABAergic neurons [29]. Other subgroups of GABAergic neurons containing SOM, NPY, nNOS and calretinin project caudally and/or locally within BF [7,8,11,29]. Some SOM and NPY neurons are likely to be sleep-active [7,50,51]. The discharge of vGluT2 neurons is weakly modulated by behavioral state [7]. They discharge faster during wakefulness and REM sleep. The calcium binding proteins Calb and Calret are expressed in subsets of glutamatergic as well as GABAergic neurons. Calb+/vGluT2+ neurons may be cortically projecting whereas calretinin neurons are not [20]. *Abbreviations*: Calb: calbindin; Calret: calretinin; ChAT: Choline acetyltransferase; GAD: glutamic acid decarboxylase; Kv: voltage-gated delayed-rectifier potassium channel; Nk3R: Neurokinin B receptors, type 3; nNOS+: neuronal nitric oxide synthase; NPY: neuropeptide Y; PV: parvalbumin; REM: rapid eye movement; SOM: somatostatin; vGluT1/2/3: vesicular glutamate transporter type 1/2/3.

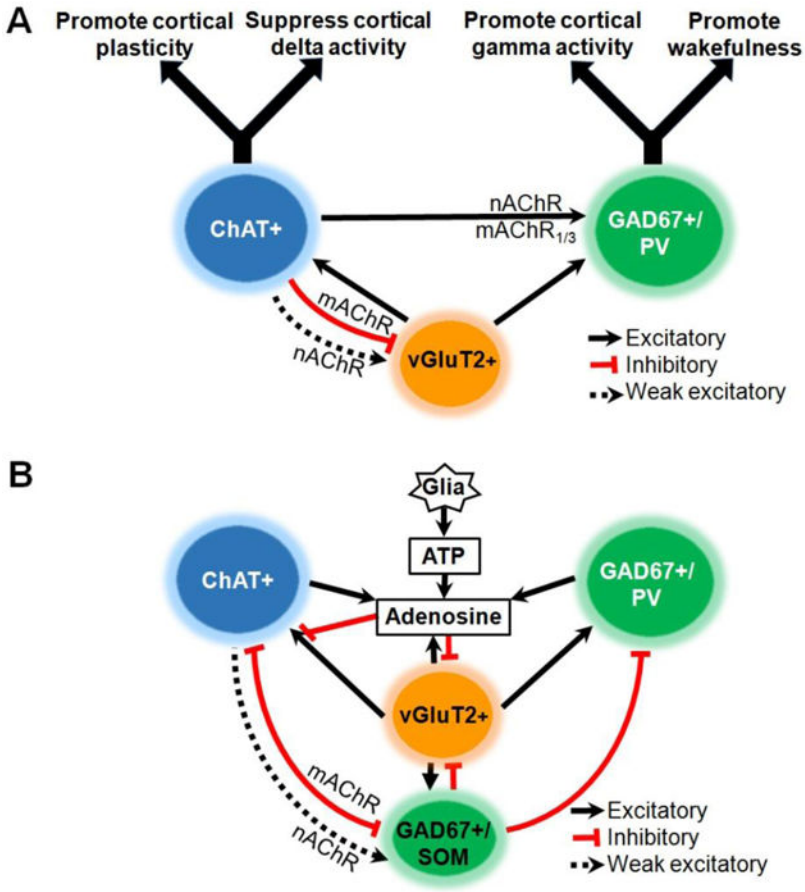

Figure 3. Models of the basal forebrain (BF) circuits controlling sleep-wake behavior

Solid lines with arrowheads indicate excitatory effects on the target neurons. The black dashed lines indicate a weak excitatory effect. Lines with flat ends indicate inhibitory effects. **A. BF circuits promoting wakefulness, cortical activation and adaptive responses to behaviorally-relevant stimuli.** Current data indicates that GABAergic projections neurons are the most important for promoting wakefulness. An important subset of these neurons containing parvalbumin (PV) regulates cortical gamma band activity. Cholinergic (ChAT+) and glutamatergic (vGluT2+) neurons promote wakefulness and cortical activation indirectly via excitatory effects on GABAergic/parvalbumin (GAD67+/PV) neurons, as well as via their direct cortical projections. Cholinergic neurons promote cortical plasticity in response to reinforcers. **B**. **BF circuitry involved in sleep promotion.** During prolonged wakefulness (i.e. sleep deprivation) there is accumulation of extracellular adenosine due to direct release from neurons as well as breakdown from the neurotransmitter/gliotransmitter, ATP. Adenosine inhibits BF cholinergic and GABAergic projection neurons by inhibiting their glutamatergic inputs via A1 receptors [47,48], thereby promoting a homeostatic sleep response. Activation of a subset of GABAergic neurons containing somatostatin may facilitate spontaneous transitions into non-REM sleep by direct postsynaptic inhibition of wake-promoting cholinergic and GABAergic neurons.

Abbreviations: ATP: adenosine triphosphate; choline acetyltransferase; GAD: glutamic acid decarboxylase; mAChR: muscarinic acetylcholine receptors; nAChR: nicotinic acetylcholine

receptor; NREM: non-rapid-eye-movement; PV: parvalbumin; SOM: somatostatin; vGluT2: vesicular glutamate transporter type 2.