

Basal Forebrain Cholinergic System and Memory

M.G. Blake and M.M. Boccia

Abstract Basal forebrain cholinergic neurons constitute a way station for many ascending and descending pathways. These cholinergic neurons have a role in eliciting cortical activation and arousal. It is well established that they are mainly involved in cognitive processes requiring increased levels of arousal, attentive states and/or cortical activation with desynchronized activity in the EEG. These cholinergic neurons are modulated by several afferents of different neurotransmitter systems. Of particular importance within the cortical targets of basal forebrain neurons is the hippocampal cortex. The septohippocampal pathway is a bidirectional pathway constituting the main septal efferent system, which is widely known to be implicated in every memory process investigated. The present work aims to review the main neurotransmitter systems involved in modulating cognitive processes related to learning and memory through modulation of basal forebrain neurons.

Keywords Acetylcholine · Learning · Modulation · Consolidation · GABA · Glutamate · Noradrenaline · Hypocretin · Orexin · Vasopressin · Oxytocin · Substance P

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1 Cholinergic System: Historical Perspective

Acetylcholine (ACh) is known as the main neurotransmitter of the parasympathetic branch (PNS) of the Autonomous Nervous System (ANS). Probably, ACh signaling evolved long before the development of a nervous system since it is well conserved in nature (bacteria, fungi, protozoa and plants), along with the machinery to synthesize and degrade it (Semba 2004). Moreover, as Gaddum has demonstrated, ACh is present in several nonneural tissues, such as the placenta, suggesting that ACh not only acts as a neurotransmitter but also serves other cellular functions (Chang and Gaddum 1933). ACh was the first neurotransmitter to be identified in 1906 by Hunt and Taveou (1906). Soon after, in the 1910s, Henry Dale demonstrated that ACh mimics the effects of parasympathetic nerve stimulation and he also established the distinction between the muscarinic and nicotinic actions of ACh (Dale et al. 1910). It was not known until the 1920s, by the famous, classical, simple and elegant experiments performed by Otto Loewi, using two frog hearts, that ACh was released upon nerve stimulation (Loewi 1921). Loewi's experiments renewed interest in the scientific community of the possibility of chemical involvement in neuronal communication. At that time, ACh had not been found to occur naturally in the body; however, Dale was excited and intrigued by the "vagusstoff" substance described by Loewi and commented to a friend:

We are still struggling with the ACh problem, which I mentioned to you when I saw you in the autumn. I am more and more convinced that the thing is there to be found, if only we can overcome the technical difficulties. (Letter, Dale to Richards, 22 March 1929, Archives of the National Institute for Medical Research, File 647; quoted in (Tansey 1991).

Later on, Dudley and Dale finally demonstrated that ACh was a natural constituent of mammalian bodies (Dale and Dudley 1929).

A seminal step in the study of ACh as a mediator of different effects was the introduction of physostigmine or eserine, a drug that inhibits the activity of the enzyme acetylcholinesterase. Heman George Fühner introduced, for the first time, physostigmine to an organ bath in which a leech muscle was suspended. With this pharmacological tool he was able to tackle the transiency of the effects of ACh and the muscle became extremely sensitive to it (Fühner 1918). For many years the eserinated leech muscle assay remained the most reproducible, sensitive method of identifying and quantifying ACh. It was not until the 1960s that more sophisticated chemical methods for detecting and measuring ACh were developed. And it was toward the end of that decade that a collaborative project between staff of the University of California and the Karolinska Institute in Stockholm, using a gas chromatography/mass spectrometry technique, was able to determine ACh in submicrogram amounts (Hammar et al. 1968).

The first evidence that ACh is released from cerebral cortex came much later. MacIntosh and Oberg were the first to demonstrate an outflow of ACh from the cerebral cortex (MacIntosh and Oberg 1955). They collected the superfusate from the cortex of anesthetized cat using a “surface cup” applied to the cortical surface using an anticholinesterase to prevent breakdown of ACh. ACh was then determined by bioassay. This technique was the forerunner of the actual microdialysis technique which makes it possible to study ACh, and also other substances, released in behaving animals.

2 Acetylcholine Receptors and Distribution

Acetylcholine is recognized by two different families of receptors, nicotinic receptors (nAChRs, ligand-gated ion channels) (Albuquerque et al. 2009) and muscarinic receptors (mAChRs, seven transmembrane G-protein-coupled receptors) (Bubser et al. 2012). So far, five different mAChRs are known (M1–M5). Each subtype has a unique distribution in central and peripheral nervous system, being expressed both pre- and post-synaptically (Levey 1993). While M1 mAChRs are predominantly expressed in all major areas of the forebrain, including the hippocampus, cerebral cortex, corpus striatum and thalamus, the M2 mAChRs are highly abundant in non-cholinergic neurons that project throughout the brain, including the hippocampus and neocortex. M3 mAChRs are widely distributed in the CNS, being found in the hypothalamus and in many other regions including the hippocampus. M4 mAChRs are mainly expressed in the corpus striatum in the CNS and on various presynaptic nerve terminals in the periphery. Finally, M5 mAChRs are distributed in the pars compacta of the substantia nigra and in the ventral tegmental area (VTA; Bubser et al. 2012).

Nicotinic ACh receptors (nAChRs) participate in a variety of physiological functions, including the regulation of neurotransmitter release and neuronal excitability (Levin 1992; Albuquerque et al. 2009). The nAChRs are well distributed in the CNS and also in the peripheral nervous system, immune system, and peripheral tissues (Albuquerque et al. 2009). To date, nine different nAChRs subunits

(α_2 – α_7 and β_2 – β_4) are known to exist in the mammalian brain, which combine as either homo- or heteromeric complexes into diverse functional pentameric structures (Albuquerque et al. 2009; Fasoli and Gotti 2015). The main subtypes functionally expressed in the brain are the α_7^* subunit-containing receptors (homo- or heteromeric) and those including both α and β subunits, named $\alpha_4\beta_2^*$ and $\alpha_3\beta_4^*$ (* indicates that nAChRs can contain other α and β subunits). 90% of the high nicotine binding sites in the brain correspond to the $\alpha_4\beta_2^*$ receptor subtype; the $\alpha_3\beta_4^*$ nAChR is found primarily in the parasympathetic ganglia and also expressed in a variety of brain areas (interpeduncular nucleus and medial habenula, VTA, BLA, among others) (Albuquerque et al. 2009; Yakel 2014). The α_7^* nAChRs are expressed on a variety of cells on the periphery, as well as in several brain regions involved in learning and memory. In the brain, the α_7^* receptors are expressed on neurons and non-neuronal cells (such as astrocytes, oligodendrocyte precursor cells, endothelial cells, and microglia) (Yakel 2014). Expression in these non-neuronal cells suggests a potential role in brain neuroprotection, inflammation, and brain immunity (Di Cesare Mannelli et al. 2015; Liu et al. 2015). Neuronal nAChRs are relatively expressed in low density in the human brain compared to mAChRs. Their distribution pattern is homogeneous and not restricted to well-defined brain cholinergic pathways. Binding studies using high affinity radioactive ligands against the nAChR help us to characterize its neuroanatomical distribution. In general terms, nAChRs are present in a variety of brain structures, with high density in the thalamus, caudate nucleus, substantia nigra, nucleus basalis of Meynert (NBM), and some areas with relatively lower levels such as the hippocampus, caudate, putamen and cortex, among others (Albuquerque et al. 2009; Ragazzino and Brown 2013).

3 Cholinergic Pathways

The central cholinergic system was mainly characterized using antibodies against the main enzyme responsible for synthesizing ACh, choline acetyltransferase (ChAT). Ten subpopulations of cholinergic neurons were identified and named Ch1–Ch10. Most of them are projecting neurons and subpopulations of interneurons. The main and most studied cholinergic neurons are those found in the basal forebrain because of its undoubted degeneration in Alzheimer’s disease (AD). The basal forebrain contains four overlapping cholinergic and noncholinergic cell groups tangled among each other. The Ch1–Ch4 nomenclature designates the cholinergic neurons within these four cell groups (Table a) (Mesulam 2004b).

Nomenclature	Cholinergic neurons associated with
Ch1	Medial septal nucleus
Ch2	Vertical nucleus of the diagonal band
Ch3	Horizontal limb of the diagonal band nucleus
Ch4	Nucleus basalis of Meynert

Experiments performed with tracers in several animal species have shown that Ch1 and Ch2 mainly innervate the hippocampal formation; Ch3, the olfactory bulb; and Ch4, the rest of the cortex and the amygdala. The Ch4 group contains, in the brain of primates, a component of the NBM. According to Mesulam, the term “nucleus basalis” designates “the cholinergic, as well as noncholinergic, components in the nucleus, whereas Ch4 designation is reserved for its cholinergic neurons” (Mesulam et al. 1983; Mesulam 2004a).

The main cortical inputs to the nucleus basalis are mostly glutamatergic, but can also be GABAergic, and they come from cortical projections from limbic and paralimbic structures, including the amygdala (Zaborszky et al. 1997). In rodents, there are projections from the VTA (dopamine), raphe nucleus (5-HT), and locus coeruleus (noradrenaline) areas reaching the Ch4 spot (Jones and Cuello 1989; Smiley and Mesulam 1999). Moreover, the nucleus basalis has receptors which recognize all these neurotransmitters. Saper (1984), proposed that the cholinergic basal forebrain system “diffusely” innervates the cortex. However, later, Zaborszky et al. demonstrated that the cholinergic and non-cholinergic projections to the neocortex are not diffuse (Zaborszky et al. 1997, 2015). They are organized into overlapping and segregated groups of neurons that may transmit information which originates in the basal forebrain to cortical areas, themselves interconnected. The results described suggest that basal forebrain—cortex projections patterns are very similar to those described for the cortico—striatal pathway (Zaborszky et al. 2015).

4 Acetylcholine and Cognitive Functions

In AD there are several signs of brain dysfunction, mainly memory loss. This loss of memory function was attributed to the profound degeneration of Ch4 neurons and loss of cortical cholinergic innervations (Mesulam 2004a). Moreover, before that, it was already known that the active ingredients of *Atropa belladonna* (Solanaceae family) in moderate doses have a great impact on memory and orientation. However, at that time, it was unknown which were the active ingredients contained in those plants. One of the first studies regarding the brain pharmacodynamics of atropine and related drugs was performed by Macht 1923. However, he did not propose a mechanism of action for their effects—the authors were aware of the parasympathetic activity of these drugs. Later on, several experiments were performed in both animals and humans, which have shown learning and memory impairments after treatment with anticholinergic drugs. Altogether, it has led to “the cholinergic hypothesis of geriatric memory dysfunction,” by Bartus et al. (1982) However, in the last decades, the role of Ach in memory has been debated (Blokland 1995; Gold 2003), mainly due to conflicting results obtained with cholinergic lesions (Easton et al. 2012).

At this point it is worth mentioning that memory is not a unitary process. It requires and relies on multiple cognitive functions supported by different brain systems and, moreover, memory requires multiple processes to be formed

(encoding, consolidation, retrieval) (Hasselmo 2006; Hasselmo and Sarter 2011). The idea that cholinergic projections from BF to the cortex are involved in synaptic plasticity leading to learning and memory is supported by several observations (reviewed in Zaborszky et al. 1999). When a subject needs to perform and learn a specific task, the enhancement of a sensory representation in the task-relevant sensory cortical area depends on activation of a specific sensory cortex-prefrontal-BF-sensory cortex loop signaling the behavioral significance of the situation.

Cholinergic neurons constitute a way station for many ascending and descending pathways, thus receiving multiple inputs. The BF Ch neurons have a role in eliciting cortical activation and arousal, and it is well established that they are mainly involved in cognitive processes requiring increased level of arousal, an attentive state and/or cortical activation with desynchronized activity in the EEG. Cholinergic neurons present in the medial septum/horizontal diagonal band project to the hippocampus, and the neurons present in the horizontal limb of the diagonal band, substantia innominata, and the peripallidal regions, project to neocortical areas, constituting the nucleus basalis magnocellularis. The different populations of BF neurons appear to be innervated by different combinations of afferents (Zaborszky et al. 1991). Therefore, the BF populations seem to be compartmentalized, each compartment being involved in different cognitive operations (Everitt and Robbins 1997)—that is, the different BF circuits may be involved in modality-specific attention.

Of particular importance within the cortical targets of BF neurons is the hippocampal cortex. The septohippocampal pathway is the main septal efferent system, which is widely known to be implicated in cognitive processes. It is a bidirectional pathway composed of three separate components: cholinergic, GABAergic, and glutamatergic fibers (Goldbach et al. 1998; Pascual et al. 2004, Farr et al. 1999). The GABAergic fibers end on hippocampal interneurons, while cholinergic projections have a wider distribution, ending on many hippocampal cell types (Pascual et al. 2004).

Recently, Dannenberg et al. (2015), described that the septohippocampal system comprises two components: a direct cholinergic projection causing increased firing of hippocampal inhibitory interneurons with concomitantly decreased firing of principal cells, and an indirect pathway involved in hippocampal theta synchronization, comprising noncholinergic neurons within the MSDB that are recruited by cholinergic neurons. Activation of both pathways causes a reduction in pyramidal neuron firing and a more precise coupling to the theta oscillatory phase. These two anatomically and functionally distinct pathways are likely relevant for cholinergic control of encoding versus retrieval modes in the hippocampus (Dannenberg et al. 2015).

The septohippocampal pathway has been implicated in every memory process investigated. A suggestive finding concerning the importance of the septo-hippocampal pathway is the fact that food-storing birds have enlarged hippocampal region (dorso-medial cortex), relative to brain and body size, when compared with the non-storers, and the volume of one of the major afferent-efferent pathways (the septohippocampal pathway) is also greater in food storing species (Krebs 1990).

The septohippocampal pathway is less active in AD (Krügel et al. 2001). In a mouse model of AD, it was shown that tau pathology presents early in the

hippocampus and basal forebrain, and several morphological and functional alterations in the septohippocampal pathway suggest that there is a disconnection between both structures in AD and that tau pathology may have a role in cholinergic neurons' degeneration (Belarbi et al. 2009).

Intracerebroventricular injections of the immunotoxin 192 IgG-saporin lesion cholinergic neurons, including those in the basal forebrain (Leanza et al. 1995; Torres et al. 1994). Rats receiving 192 IgG-saporin displayed a significant delay-dependent decline in performance, indicating that this pathway is implicated in short-term memory processing. Administration of the mAChR blocker scopolamine (0.5 mg/kg, i.p.) produced more pronounced impairment in the performance of the normal control rats across all delays, and also induced further impairment in animals with 192 IgG-saporin lesions (Winters and Dunnett 2004).

After a dorsal septohippocampal pathway lesion, BF grafts allow successful cholinergic reinnervation of hippocampal neurons, but do not enhance cognitive functions in rats, and may also have adverse effects after partial septohippocampal system lesions (Dalrymple-Alford 1994). This might indicate that although these grafts reinnervate hippocampus, they probably fail to incorporate into circuits, suggesting that appropriate modulation of BF neurons by afferents appears to be critical for their activity.

5 Modulation of Cortical Projecting Cholinergic Neurons

The cholinergic neurons of the BF providing the major source of the diffuse cortical innervation are the Ch4 subgroup. Some cortical innervation (to medial prefrontal cortex, for example) also appears to be provided by Ch1–3, arising from the medial septum and the diagonal band (Eckenstein et al. 1988; Lamour et al. 1984). The stimulation of Ch4 neurons increases cortical release of ACh, thus causing desynchronization of the electroencephalogram. These cholinergic neurons are modulated by several afferents of BF, corresponding to different neurotransmitter systems.

6 GABA

The administration of GABAA agonists decreases cortical ACh release (Scatton and Bartholini 1982) by inhibiting the firing of cholinergic neurons (Khateb et al. 1998). The intra-NBM administration of the GABAA agonist muscimol impairs performance in the reference and working memory components of rats' performance in a Y-maze task (Smith et al. 1994). GABAA antagonists produce opposite effects (Bertorelli et al. 1991). Cognitive effects observed after the administration of GABAA-modulating drugs correlate with the expected behavior of this pathway. For example, the administration of FG7142 (N-methyl-betacarboline- 3-carboxamide, a partial agonist of the BZD binding site of the GABAA receptor) in the

NBM, increases ACh release to the cortex (Fadel et al. 1996; Moore et al. 1995), and enhances performance on the working memory components of a double Y-maze task (Smith et al. 1994).

However, the administration of the GABAA receptor agonist muscimol and the antagonist bicuculline impairs long-term memory consolidation, but not acquisition, of an inhibitory avoidance memory in rats (Morón et al. 2002). The administration of the cognitive enhancer NS-105 ((+)-5-oxo-D-prolinepiperidinamide monohydrate) reverses the amnesic actions caused by cholinergic dysfunction in a variety of animal models (Ogasawara et al. 1999), enhancing cholinergic neuronal activity by the suppression of GABAB receptor-mediated responses.

GABAergic modulation of cholinergic BF neurons, and also GABAergic projecting neurons from BF, is involved not only in cognitive processes, but also in the sleep-wake cycle.

7 Glutamate

Glutamatergic agonists administered in the NBM increase cortical ACh release (Kurosawa et al. 1989), via stimulation of cholinergic neurons, apparently through AMPA receptors (Page et al. 1993; Weiss et al. 1994; but see also Rasmusson et al. 1996). Again, these pharmacological effects appear to be correlated with behavior. In rats subjected to a task in which darkness is associated with the opportunity to consume a sweetened pellet, the intra-NBM administration of NMDA following exposure to darkness/cereal stimulus potentiated both the magnitude and duration of stimulated cortical ACh release (Fadel et al. 2001). Moreover, kynurenate, a normal product of the metabolism of the amino acid L-tryptophan that blocks ionotropic glutamate receptors (Elmslie and Yoshikami 1985), reduced ACh release in the prefrontal cortex in rats subjected to this task (Fadel et al. 2001).

Glutamatergic modulation of BF cholinergic neurons activity appears to be critical for AD progression. In this sense, A β 1-42 increases glutamate levels in the synaptic cleft by inhibiting the astroglial glutamate transporter, thus increasing intracellular Ca²⁺ levels (Harkany et al. 2000), through enhancement of NMDA receptor activity (Molnár et al. 2004), although other possible mechanisms have been proposed. Such glutamate dysregulation has a profound impact on the selective degeneration of BF cholinergic neurons in the early stage of AD, and constitutes the rationale for the clinical use of memantine, a moderate affinity uncompetitive NMDA receptor antagonist that does not interfere with normal NMDA receptor function (Chen and Lipton 2006). It was also shown that activation of metabotropic glutamate receptor mGluR7 protected BF neurons from NMDA-induced excitotoxicity. This protective effect of mGluR7 activation on BF cholinergic neurons is selectively impaired by A β accumulation. Hence, this fact suggests an additional potential basis for the A β -induced disruption of calcium homeostasis (Gu et al. 2014).

8 Catecholamines

Noradrenergic inputs to the BF seems to arise from collateral connections to cholinergic neurons branching from an ascending visceral projection system (Knox et al. 2004) which cause depolarization and spike-discharges in cholinergic neurons through α_1 adrenergic receptors (Fort et al. 1995). The majority of noradrenergic input to medial septal area, the medial preoptic area, and the substantia innominata is ipsilateral and provided by the locus coeruleus (España and Berridge 2006), degeneration of locus coeruleus neurons has been linked to age-related dementia (Chan-Palay 1991; Palmer and DeKosky 1993) and to AD progression (German et al. 1992). It was shown that this degeneration of locus coeruleus neurons correlates with amyloid plaque formation and neurofibrillary tangles in the areas receiving projections from the locus coeruleus, and also correlates with the severity of dementia (Bondareff et al. 1987), thus suggesting a protective role for noradrenergic innervation of these areas (Heneka et al. 2006). Indirect evidence of a behavioral correlation with this innervation arose from experiments performed with the neurotoxins 6-OH-DA and DSP-4 in an inhibitory avoidance task (Cornwell-Jones et al. 1989), in a radial arm maze task (Heneka et al. 2006), and in a social partner recognition test (Heneka et al. 2006). DSP-4 causes hippocampal and cortical depletion of monoamines, but leaves BF monoaminergic neurotransmission less affected (Fritschy and Grzanna 1989), allowing adrenergic modulation of cholinergic neurons at this level. Catecholaminergic enhancing effects on arousal are exerted by modulation of BF cholinergic neurons (Lelkes et al. 2013). This modulation of BF cholinergic neurons is also involved in non-REM sleep suppression, although these neurons seem not to be implicated in the REM-sleep suppressing effect of noradrenaline (Lelkes et al. 2013).

Specifically regarding the septohippocampal pathway, septal neurons are modulated by catecholamines. Dopamine exerts a negative modulatory effect on cholinergic septal neurons. Lesions of dopaminergic afferents by 6-hydroxydopamine lead to a disinhibition of cholinergic neurons, causing a specific increase in cholinergic hippocampal activity in mice (Galey et al. 1989), enhancing spatial discrimination performance related to improved working memory (but not reference memory) in an 8-arm radial maze. On the contrary, norepinephrin modulates these neurons positively through alpha receptors. In this sense, the intra-septal administration of phenoxybenzamine (an alpha-noradrenergic blocker), impairs the cholinergic activation induced by retrieval, causing a selective working memory deficit in the 8-arm radial maze (Marighetto et al. 1989).

9 Acetylcholine

Cholinergic innervation of the basal forebrain neurons comes from the peduncle-pontine tegmentum (PPT), the Ch5 group of Mesulam et al. (1983, 1993). These efferents exert widespread control over neocortical EEG activity and aid the maintenance of high-frequency EEG activation during waking and REM sleep. Stimulation of Ch5 neurons with 100 Hz for 2 s, causes EEG desynchronization, an effect markedly reduced by blockers of neural firing (tetrodotoxin, procaine, lidocaine) and also by blockers of synaptic transmission (calcium-free solution plus magnesium or cobalt) on BF cholinergic neurons (Rasmusson et al. 1994; Dringenberg and Olmstead 2003). Although this desynchronizing effect of Ch5 group stimulation involves relays not only in the BF but also in the central thalamus, the BF is the predominant structure (Dringenberg and Olmstead 2003). Infusion of the glutamate antagonist kynurenate within the NBM also reduces the EEG desynchronization elicited by PPT stimulation, suggesting that the major excitatory input to the cholinergic neurons of the NBM from the PPT is exerted via modulation of glutamatergic synapses (Rasmusson et al. 1994), and it has been proposed that M2 presynaptic receptors of glutamatergic neurons of the BF might be involved (Bertorelli et al. 1991; Sim and Griffith 1996).

10 Hypocretin/Orexin and Adenosine

Another major modulatory system of BF involves the orexin neurons, which project widely throughout the CNS. Orexin system projections in the BF modulate cortical ACh release, a fact that could be important for the cognitive components of motivated behavior such as the behavioral adaptation to food deprivation by promoting the detection and selection of stimuli related to physiological needs (Fadel and Frederick-Duus 2008). Orexin/hypocretin also modulates hippocampal function by direct inputs to hippocampal neurons, and a robust innervation of medial septum cholinergic neurons, a pathway that appears to play a critical role in attention (Fadel and Burk 2010). Additionally, orexin/hypocretin release in BF or directly in the hippocampus caused increased GABA and glutamate release from hippocampal neurons. Aging is accompanied by a significant reduction in orexin fiber innervation of GABAergic neurons in the BF, while the direct hippocampal innervation remains unaltered (Stanley and Fadel 2011). This alteration in innervation of BF might contribute to age-related cognitive dysfunctions.

This neuromodulatory system interacts with the neuroregulator adenosine. Adenosine is considered a sleep/wake cycle homeostatic regulator, because a significant increase in extracellular adenosine levels is observed after prolonged wakefulness in specific areas of the brain, particularly the BF and cortex (Porkka-Heiskanen et al. 2000; Basheer et al. 2001, 2007; Kalinchuk et al. 2011). Adenosine promotes sleep by an A1 receptor-mediated inhibition of glutamatergic inputs to

cortically projecting cholinergic and GABA/PV neurons. Conversely, blockade of A1 receptors in the BF promotes attentive wakefulness by promoting the high-frequency oscillations in the cortex required for attention and cognition (Yang et al. 2013).

11 Vasopressin and Oxytocin

The two neurohypophyseal hormones have also been proposed to modulate the firing of BF cholinergic neurons. In the human forebrain, the distribution of receptors differs between vasopressin and oxytocin, but they overlap in the brainstem. Vasopressin receptors are present in the dorsal part of the lateral septal nucleus, in midline nuclei and adjacent intralaminar nuclei of the thalamus, in the hilus of the dentate gyrus, and the dorsolateral part of the basal amygdaloid nucleus (Loup et al. 1991). Oxytocin receptors are observed in the NBM, the nucleus of the vertical limb of the diagonal band of Broca, the ventral part of the lateral septal nucleus, the preoptic/anterior hypothalamic area, the posterior hypothalamic area, and variably in the globus pallidus and ventral pallidum (Loup et al. 1991). The presence of oxytocin and vasopressin binding sites in all these areas suggests they play a neuromodulatory role in the central nervous system, probably by modulating cholinergic transmission in the BF. In this sense, the administration of oxytocin to Swiss mice impairs consolidation of avoidance memory, and this impairment is prevented by the anticholinesterase drug physostigmine. Additionally, blockade of oxytocin receptors enhances memory consolidation in mice, an effect blocked by antagonists of central cholinergic receptors (muscarinic and nicotinic), suggesting that oxytocin modulates ACh release in downstream neurons related to consolidation of avoidance memory (Boccia and Baratti 2000). Following the same line, arginine-vasopressin enhances memory consolidation of an avoidance memory through V1 receptors, and an antagonist of these receptors impairs memory (Boccia et al. 1998; Tanabe et al. 1999). These effects of vasopressin seem to be exerted by positively modulating ACh release in cholinergic neurons, since vasopressin reversed the memory deficit caused by administration of scopolamine either in an inhibitory avoidance in mice (Tanabe et al. 1999), and in an eight-arm radial maze in rats (Mishima et al. 2001).

12 Substance P

Substance P is a neurokinin widely distributed in the brain, particularly important in the hippocampus, diencephalon, BF cholinergic neurons, and in the amygdala (Ribeiro-da-Silva and Hökfelt 2000). Substance P administered in the NBM (Huston and Hasenöhr 1995) or in the medial septal nucleus (Stäubli and Huston 1980) exerts memory enhancing effects. The related modulator neuropeptide K also

enhances memory retention when injected into the rostral and caudal portions of the hippocampus and the amygdala, but exerts no effect when injected into the septum (Flood et al. 1990).

13 Neuropeptide-Y

Neuropeptide-Y (NPY) is present both in local neurons as well as in fibers in the BF, particularly in the more caudal areas, and has been proposed to have a role in locomotor activity, eating behavior, stress responses, memory processing, blood pressure, some neuroendocrine functions, and also in the integration of sleep and behavioral stages via the BF (Tóth et al. 2007; Wettstein et al. 1995). Neuropeptide Y was proven to be affected in AD, and there is also clinical evidence for its implication in depression, schizophrenia and anorexia nervosa, among others (Wettstein et al. 1995; Eaton et al. 2007). NPY-containing neurons have wide axonal arborizations, and they are believed to modulate the GABA/Ach interactions in the BF. NPY enhanced avoidance memory in a T-maze in mice when administered into the rostral portion of the hippocampus and septum, but impaired retention when injected in the caudal portion of the hippocampus and amygdala, and its interaction with the central cholinergic system is evidenced by its ability to reverse scopolamine-induced amnesia (Flood et al. 1987, 1989). These effects of NPY on memory retention appear to be mediated through presynaptic (Y2) NPY receptors (Flood and Morley 1989). It was also reported that septal cholinergic efferents in the dentate gyrus exert a powerful modulation of NPY-containing interneurons (Dougherty and Milner 1999). In a colchicine-induced AD-like condition in rats (a rat model of AD) intracerebroventricular administration of nicotine induces reversal of amnesia in a Morris water maze (Rangani et al. 2012). The administration of NPY mimics nicotine effects, whereas an NPY-Y1 receptor antagonist impairs the nicotine-induced reversal of amnesia (Rangani et al. 2012), showing that the memory enhancing effects of ACh through nicotinic cholinergic receptors may be mediated, at least in part, by NPY interneurons. Regarding the possible involvement of NPY signaling on AD, it was found that intracerebroventricular administration of aggregated A β (1–40) induced depressive-like behavior and spatial memory impairment, but these effects were prevented by pretreatment with NPY, and these effects are probably mediated by NPY-Y2 receptors (dos Santos et al. 2103). Thus, this peptide has a relevant physiological role as a modulator of memory processing within the BF and the hippocampus.

14 Galanin

Galanin is widely distributed within the central and peripheral nervous system, exerting behavioral and non-behavioral actions. In the BF neurons of the nucleus basalis of Meynert/medial septum/diagonal band innervating the cerebral cortex and

hippocampus, galanin is an inhibitory modulator of cholinergic transmission (Crawley 1996). Galanin does not colocalize with ACh in the BF of humans and great apes, but it does in monkeys, suggesting that an evolutionary change occurred in galanin-ACh coexistence within the primate BF, at the branch point between monkeys and apes (Benzing et al. 1993). The degree of cognitive decline observed in elderly patients is highly correlated with the magnitude of the reduction in central cholinergic activity, independent of age (Bartus et al. 1982; Francis et al. 1999), and the same applies for AD patients (Bierer et al. 1995; Neugroschl and Wang 2011; Querfurth and LaFerla 2010). Among all of them, the most consistent marker of neuronal loss in AD is the decline in number of cholinergic neurons of the NBM (Coyle et al. 1983). Dramatic reductions in ChAT and AChE are routinely seen in postmortem samples of BF and cortical samples from AD patients, as compared to age-matched controls (Bierer et al. 1995). Also, cholinergic nicotinic receptors were found to be reduced in 30–40%, mainly due to a reduction of the $\alpha_4\beta_2$ subtype, with relative preservation of the α_7 -nicotinic receptors (Court et al. 2001; Perry et al. 1995). However, cholinergic dysfunction does not provide a complete account of age-related cognitive deficits, and age-related changes in cholinergic function typically occur within the context of changes in several other neuromodulatory systems (Decker and McGaugh 1991). Remarkably, in post-mortem studies performed in the BF of AD patients, galanin concentrations are much higher in the NBM than in age-matched controls (Beal et al. 1990). Histological analyses show that galanin hyperinnervates cholinergic neurons in the BF in AD patients, and this hypertrophic network widens with the severity of AD symptoms (Chan-Palay 1988; Mufson et al. 1993). Galanin injected in the medial septum/diagonal band, inhibits ACh release in the hippocampus, *in vivo* and *in vitro* (Fisone et al. 1987), and this effect is blocked by galanin receptor blockers (Bartfai et al. 1991). It appears that this inhibitory effect of galanin on cholinergic projecting neurons is exerted by interaction with presynaptic receptors (Dutar et al. 1989), and occurs physiologically only at high discharge frequency (Hökfelt et al. 1987). That is, endogenous galanin inhibits ACh release only when the neuron is firing at high rates, and this is hypothesized to happen during the progressive loss of the large majority of BF cholinergic neurons in AD (Hökfelt et al. 1987).

Behavioral effects observed after administration of galanin are in accordance with these observations. In this sense, centrally administered galanin has inhibitory actions in several rodent learning tasks. Galanin was reported to impair learning in a Morris water maze (Sundström et al. 1988), in a one-trial discriminative reward learning task with a starburst five-arm radial maze (Malin et al. 1992), in a delayed nonmatching-to-sample task (Robinson and Crowley 1993a, b), in the latter case aggravating a deficit caused by a muscarinic cholinergic receptor antagonist, and in a step-down inhibitory avoidance task (Ukai et al. 1995). In the latter case, the impairing effect of galanin was reversed by improving cholinergic system signaling. Intra-septal administration of galanin also impairs performance in a spontaneous alternation task in rats, an effect that can be ameliorated by co-administration of glucose (Stefani and Gold 1998). Galanin antagonists were reported to enhance learning in a Morris water maze (Ogren et al. 1992).

Galanin administered in the medial septum decreases choice accuracy in a working memory task in a T-maze, and also decreases hippocampal theta activity recorded from the dentate hilus in a dose-dependent manner (Givens et al. 1992).

Galanin overexpressing transgenic mice exhibit cognitive and neurochemical deficits similar to those occurring in AD: they show learning and memory deficits, impaired long-term potentiation, reduced hippocampal excitability, lower evoked glutamate release, and reduced numbers of cholinergic neurons in the horizontal limb of the diagonal band compared to wild type mice (Crawley et al. 2002).

It is undoubtedly true that galanin exacerbates cognitive impairment in AD. However, galanin hyperinnervation promotes BF cholinergic neuronal function and survival (Ding et al. 2006; Elliott-Hunt et al. 2004). Galanin also exerts neuroprotective effects in rodent models of neurotoxicity, supporting the idea that galanin may delay the onset of symptoms of AD (Counts et al. 2010).

There is also evidence for the existence of interactions between galanin receptors and NPY receptors in the nucleus of the solitarii tract, hypothalamus and dorsal raphe nucleus, and it has been suggested that these interactions might exist in other areas, serving to equilibrate the physiological actions of the two receptors (Díaz-Cabiale et al. 2014).

15 Concluding Remarks

Modulation of basal forebrain cholinergic neurons by neurotransmitter systems critically modifies cognitive functions, including learning and memory processes. Although loss of these cholinergic neurons occurs during the progression of AD, neurons also degenerate in several nuclei projecting to the basal forebrain, making it hard to distinguish causes from consequences. Increasing knowledge of these modulatory systems allows the discovery of pharmacological targets, important for ameliorating AD cognitive symptoms.

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