A Summary of Electrophysiological Research of Basal Forebrain Cholinergic Neurons*

Bazal Önbeyin Kolinerjik Hücrelerinin Elektrofizyolojik Analizi

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Abstract

Acetylcholine has been known to be a wake-promoting neurotransmitter since the earliest microdialysis studies coupled to electroencephalographic (EEG) measurements. Advances in electrophysiological recording tools tied to anatomical identification methods helped to unequivocally indicate that these neurons exhibit augmented activity during wake periods. Later studies have revealed that acetylcholine plays essential roles in higher cognitive functions such as learning and memory. Understanding the intrinsic and synaptic electrophysiology of basal forebrain cholinergic (BFc) neurons is of paramount importance for answering how the BFc neuron system fulfills all those functions. This review discusses the latter questions along with a summary of missing links in the current state of knowledge.

Keywords: Acetylcholine, neuron, neuromodulation, electrophysiology

Öz

İlk mikrodiyaliz ve elektoensefalogram (EEG) çalışmalarından beri asetilkolinin bilinç üzerindeki uyarıcı etkileri bilinmektedir. Elektrofizyolojik tekniklerdeki ilerlemeler ve bu tekniklerin anatomik metodlarla harmanlanması sayesinde asetilkolinin uyanıklık süreçlerindeki rolü hakkında geçmiş bulguları destekleyici ve genişletici bilgilere ulaşılmıştır. Uyku/uyanıklık regülasyonuna ek olarak, asetilkolinin öğrenme ve bellekteki önemli rolü de yeni çalışmalarda desteklenmektedir. Kortekse asetilkolin girdisini sağlayan bazal önbeyindeki kolinerjik hücrelerin hem içsel hem de sinaptik elektrofizyolojik özelliklerini anlamak bu bağlamda çok önemlidir. Bu derleme makalesinde, bazal önbeyin kolinerjik hücreleri hakkındaki elektrofizyolojik bulgular ve literatürdeki eksiklikler tartışılmaktadır.

Anahtar Sözcükler: Asetilkolin, nöron, nöromodülasyon, elektrofizyoloji

INTRODUCTION

Historical Context

Cortical areas across the mammals are covered with cholinergic axons. To give some examples, Descarries et al. (2004) estimate that total cholinergic axonal lengths in the rat neocortex reach levels as long as 7.6 km. Given accounts that report 4 varicosities per 10 µm in cholinergic fibers reveals around 30 billion acetylcholine release sites just in the neocortex of the rat (Descarries et al., 2004). Previous ultrastructural data revealed that cholinergic appositions in the neocortex are not associated with a synaptic morphology (Umbriaco et al., 1994; Mrzljak et al. 1995; Smiley et al. 1997). This led to the thinking that acetylcholine exerts its actions mainly through volume transmission. Nonetheless, recent ultrastructural studies combined with immunohistochemical labelling of synaptic markers such as neuroligin 2 and gephyrin clearly demonstrated that the majority of cholinergic varicosities form synapses in the areas they innervate (Takács et al., 2013; 2018). Moreover, optogenetic studies have revealed that postsynaptic effects of acetylcholine cannot be readily mimicked by adding cholinergic agonists (Unal et al., 2015), an argument against volume transmission hypothesis. The limited spatial innervation by single cholinergic axons in the cortex further supports the specificity of this system (Li et al., 2018). Thus, acetylcholine transmission is likely to be of synaptic nature with a general topographic

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organization: this requires the endowment of cholinergic neurons with the capability to adapt to dynamic changes in brain states. This necessitates the careful investigation of the physiology of basal forebrain cholinergic (BFc) neurons. Before a consideration of the physiology of BFc neurons, a brief overview of the historical context and anatomical descriptions would be instrumental in providing us with a framework from which we can view the functional aspects of these neurons.

First anatomical accounts of the basal forebrain started with the beginning of the 19th century where the subcommisural area was named as the unnamed substance (substantia innominata) by Johann Christian Reil (Zaborszky et al., 2011). Afterwards, the German anatomist Karl Bogislaus Reichert considered the basal forebrain as a discrete brain region in a human brain atlas (Zaborszky et al., 2011). Subsequently, Theodor Meynert made a description of hyperchromatic cells within this region followed by the full topographical descriptions from von Kolliker, who named the BF after Meynert as the "nucleus basalis of Meynert".

These anatomical descriptions are considered to be accurate even today (for more detail, refer to Zaborszky et al., 2011). With the start of the 20th century, physiological research on chemicals involved in cell to cell communication gained impetus and for the first time, the physiological effects of acetylcholine were described by the groundbreaking studies of Dale and Loewi (see Rubin, 2007). In the middle of the 20th century, work by Katz and his co-workers characterized acetylcholine's actions in the neuromuscular junction for the first time (Katz and Miledi, 1966). In parallel, Eccles et al. (1954) characterized acetylcholine's actions for the first time within the central nervous system: they have found the nicotinic excitation of Renshaw interneurons within the spinal cord and how it leads to the inhibition of motor neurons.

Around the same time, based on the similarity of the morphological make up between brainstem and BF neurons, the BF was considered as an extension of the brainstem activating system that is implicated in cortical arousal (Reviewed in Zaborszky et al., 2011). These notions led to studies that considered BF's role in cortical activation. With the development of antibodies for choline acetyltransferase (ChAT) and tract tracing techniques, it became widely accepted that the BF harbors cholinergic neurons (BFc neurons) that send heavy projections to diverse cortical areas (see Semba, 2004). Microdialysis studies coupled with cortical electroencephalographic (EEG) recordings have revealed that acetylcholine release exhibits an enhancement during cortical arousal (Kanai and Szerb, 1965). Complementing these findings, pharmacological studies by Krnjevic and Phillis (1963) provided strong support regarding the excitability enhancing function of acetylcholine in the cortex. Later research have shown that EEG measures involve more than the measurement of general arousal, acetylcholine's role in higher cognitive functions came to be widely appreciated (e.g. Colangelo et al., 2019).

A Brief Overview of the Anatomy

The BF is made up of cytoarchitectonically heterogeneous areas situated in the ventromedial forebrain. The areas that make up the BF and their projections are listed on Table 1. These areas communicate with the rest of the brain through medial forebrain bundle, ventral amygdalofugal pathway, diagonal band of Broca, and the inferior thalamic peduncle (Heimer and Alheid, 1991).

Table 1: Main outputs of different BFc neurons found in different BF subregions (Luskin and Price, 1982; Amaral and Kurz, 1985; Henny and Jones, 2006; Zaborszky et al., 2011).

The BF Area	Main outputs
Medial Septum / Ventral diagonal band complex (MS/VDB)	Hippocampus
Horizontal diagonal band (HDB)	Olfactory buld, piriform cortex, entorhinal cortex, lateral hypothalamus
Substantia innominata (SI)	Basolateral amygdala (BLA), neocortex
Magnocellular preoptic area (MCPO)	Olfactory buld, piriform cortex, entorhinal cortex, lateral hypothalamus
Ventral pallidum (VP)	BLA, neocortex
Extended amygdala (EA)	BLA, neocortex
Ansa lenticularis	BLA, neocortex

The BF outputs to neocortical areas are not well-reciprocated: cortical feedback to the BF arises almost exclusively from prefrontal cortical areas (Mesulam and Mufson, 1984; Zaborszky et al., 1997). Recent evidence indicates that the prefrontal cortical input is largely on non-cholinergic cells with BFc neurons receiving minimal direct input from these regions (Gielow et al., 2017).

Subcortical inputs reach areas rich in BFc neurons from the ascending neuromodulatory nuclei that involve norepinephrine (Zaborszky et al., 1993), epinephrine (Hajszan and Zaborszky, 2002), dopamine (Grove, 1988; McDonald, 1991; Petrovich et al., 1996), and serotonin (Gasbarri et al., 1999; Leranth and Vertes, 1999; Hajszan and Zaborszky, 2000) along with inputs from various hypothalamic nuclei (Cullinan and Zaborszky, 1991).

ELECTROPHYSIOLOGY of BFc NEURONS

In vivo studies

Understanding the functional physiology of BFc neurons requires the researchers to concomitantly record cortical EEG signals and single BFc unit activity for delineating the reciprocal relationship between BFc neurons and different cortical regions. Another challenge involves the heterogeneity of the BF as an anatomical entity: BF does not only contain cholinergic (BFc) neurons. BFc neurons are intermingled with noncholinergic BF neurons, expressing a variety of peptides and calcium binding proteins (Zaborszky and Duque, 2000). One way to deal with that challenge involves juxtacellularly labelling neurons during recordings followed by post hoc ChAT immunohistochemistry. In line with the expectations from pharmacological studies implicating acetylcholine in increased neural excitability and elevated acetylcholine release during alertness states (Meller et al., 2019), Manns et al. (2000) revealed increased BFc neuron firing in nucleus basalis during desynchronized (i.e. "activated") retrosplenial cortical activity (Manns et al., 2000). The unit

discharges were seen to occur in bursts suggesting that BFc neurons have a burst generating mechanism. Spike triggered averages acquired in this study revealed a strong cross correlation between cortical theta rhythms and unit bursts, suggesting a uni-directional information flow from the BF to the cortex (Manns et al., 2000). Similar results were obtained by Lee et al. (2005) who recorded BFc neurons from the magnocellular preoptic nucleus and substantia innominata while recording EEG signals from retrosplenial cortex. Simon et al. (2006) recording from medial septal BFc neurons along with hippocampal local field potentials (LFPs) did not find evidence for BFc neuron unit activity phase locked with hippocampal theta. These authors also did not find evidence for bursting in BFc neurons (Simon et al., 2006). In a similar vein, Duque et al. (2000) also did not report action potential bursts in BFc neurons under different experimental conditions involving records of spontaneous activity and tail pinch associated changes in arousal (Duque et al., 2000). When these authors assessed correlations between single unit activity and zero-crossing in EEG epochs, a bidirectional relationship between BFc neurons and cortical activity was revealed: when the peak frequency band was restricted around 1 Hz, cortical arousal preceded BFc neuron activity while the opposite was true at peaks of beta and delta frequencies.

More recent studies implemented optogenetic identification of BFc neurons in vivo in behaving mice. Evidence indicates that BFc neurons encoded primary rewards and punishments in sustained attention tasks (Hangya et al., 2015). Studies implementing microendoscopic calcium measurements have shown that BFc neurons take part in different phases of behavior (i.e. before running and licking onsets and in the presence of discrete punishments) when compared to noncholinergic BF neurons (Harrison et al., 2016; Tashakori-Sabzevar and Ward, 2018).

Overall, these studies indicate that BFc neurons are selectively active during increased cortical arousal and they encode distinct behavioral states as compared to their noncholinergic counterparts. A major discrepancy among in vivo studies appears to involve bursting. As alluded to before, bursting behavior is observed in some studies but not others. It is important to note that these studies focused on different BFc regions: studies from more posterior regions of the BF report bursting BFc neurons (Manns et al., 2000; Lee et al., 2005) while this mode of activity is not encountered in studies focusing on more anterior regions (Duque et al., 2000; Simon et al., 2006). Thus, there are some potential interregional differences in terms of intrinsic membrane properties and/or inputs. Unfortunately, in vitro studies (reviewed below) did not provide an explanation for these discrepancies so far.

In vitro studies: Studies on membrane properties

Initial identification efforts during in vitro studies entailed a reliance on acetylcholinesterase staining (AChE) following biocytin fillings in acute slices containing the MS and vDB (Griffith and Matthews, 1986). Subsequent experiments made use of the ChAT antibody (Markram and Segal, 1990). Both approaches revealed that unlike their noncholinergic counterparts, BFc neurons exhibit slower firing discharge proceeded by a conspicuous slow afterhyperpolarization (S-AHP). Some later studies relied on these electrophysiological criteria along with the bigger size of BFc neurons in BF slices and cultures (Allen et al., 1993; Garrido-Sanabria et al., 2011). However, the convergence of data from experiments using AChE and ChAT staining constitutes problems as AChE is not exclusively found in BFc neurons. Another problem with this post hoc immunohistochemical approach involves false negatives due to washout of proteins. Indeed, numerical estimates from anatomical studies exceed the proportion of BFc neurons recorded in vitro (Henderson et al., 2001). Conversely, soma size did not constitute a reliable criterion as some noncholinergic BF neurons, some of which are neuropeptide Y positive, appear to be indistinguishable from BFc neurons in this respect (Duque et al., 2007).

Another approach entails injecting cy3 conjugated p75 antibodies in vivo to pre-label BFc neurons as a proportion of BFc neurons express this marker (Wu et al., 2000). Single cell RT-PCR has been another approach to test the ChAT positivity of recorded neurons in slices (Sotty et al., 2003) and cultures (Han et al., 2002). In the former case, p75 negative BFc neurons get missed while in the latter case, false positives are possible due to unintentional collection of ChAT from the neurons that are not being recorded.

Thus, older studies differed in their methods ominously which might have added to the a lack of a unified view of BFc neuron physiology. These complications might be further amplified by studies that focus on different BF subregions. With the development of transgenic mice allowing the utilization of reporter proteins, researchers began to record BFc neurons with better ease. Transgenic mice in which green fluorescent protein is expressed under the promoter of ChAT gene (Unal et al., 2012; Lopez-Hernandez et al., 2017) is currently the state of the art method for characterizing BFc neurons in vitro. When these studies are taken into account along with older studies, certain universal features for BFc neurons started to emerge.

The most consistent result pertains to the excitability of BFc neurons: they are the least excitable neuron population in the basal forebrain with slowest firing rates (Griffith et al., 1991). There are contradictory reports regarding their spontaneous activity but current injection evoked firing does not typically exceed 10 Hz in these neurons. The firing rates are largely limited by the presence of prominent afterhyperpolarizations, largely mediated by SK-channels, and lower input resistances (Unal et al., 2012). In addition to that, some BFc neurons exhibit a noticeable delay of firing when depolarized from a hyperpolarized potential (Eggermann et al., 2001; Unal et al., 2012) while some do not exhibit this delay (Unal et al., 2012). Unal and his colleagues classified these neurons as early- (EF) and late-firing (LF) neurons based on the action potential delay they exhibit from negative potentials. These researchers have found that the properties of the transient potassium currents in these cells correlate with action potential delay only in LF BFc neurons while no such correlation was found in EF BFc neurons. Actually, EF and LF BFc neurons did not differ significantly along any dimension related to

transient potassium currents, which are typically known to delay action potential firing in neurons (e.g. Adams et al., 2019); this finding seems to stem from differences in the density of low-voltage activated calcium (LVA Va Ca2+) current density in these neurons where higher density of these currents masked the transient potassium current's action potential delaying function specifically in EF BFc neurons.

At more hyperpolarized potentials, BFc neurons display inward rectification and unlike most of their noncholinergic counterparts they do not exhibit h-currents (McKenna et al., 2013). One major inconsistency that is also encountered in the in vivo literature pertains to bursting behavior in BFc neurons. This pattern in vitro is consistently reported by different researchers from the laboratory of Dr. Barbara Jones who studied the behavior of BFc neurons from substantia innominata of guinae pigs (Khateb et al., 1992; 1997; Alonso et al., 1996; Eggermann et al., 2001). These studies reported rhythmic bursts (augmented by NMDA agonists) in these cells with an intra-burst incidence ranging from 100 to 200 Hz at hyperpolarized potentials when BFc neurons are hyperpolarized along with a switch to tonic firing at more depolarized membrane potentials, similar to thalamic neurons (Iavarone et al., 2019). These findings might be related to interregional and species differences and need to be addressed in future studies recording from multiple BF regions at once.

In vitro studies: Studies on inputs

Ultrastructural studies coupled to tract tracing have revealed that BFc neurons receive inputs from striatum, amygdala, hypothalamus, and brainstem along with inputs with a variety of neuromodulatory systems that include noradrenaline, adrenaline, and dopamine. Furthermore, these neurons receive local inputs from neuropeptide Y, encephalin, substance P,and somatostatin positive BF neurons (Zaborszky et al., 2018). Both pharmacological and optogenetic studies have tested the functions of some of these inputs.

Momiyama and Zaborszky (2006) have revealed that bath application of somatostatin results in reduced GABAergic and glutamatergic inputs, suggesting a presynaptic function for this neuropeptide. An optogenetic study has shown that somatostatin positive BF neurons inhibit BFc neurons through GABAergic mechanisms as well (Xu et al., 2015), suggesting that somatostatin neurons in the BF are sleep active neurons that counteract BFc neuron activity. It would be interesting to investigate whether inhibition imposed by somatostatin BF neurons is reciprocated by BFc neurons.

Orexin, a neuromodulator associated with waking (Burk et al., 2019; Chowdhury et al., 2019) has shown to have an excitatory effect in BFc neurons (Wu et al., 2004) possibly through an increased sodium conductance accompanied by the inhibition of inward rectifier. In addition, research has shown that activation of BFc neurons increase GABAergic inhibition back into these neurons forming an inhibitory feedback loop, an effect counteracted by galanin which has the ability to suppress GABAergic inputs onto BFc neurons under a variety of conditions (Damborsky et al., 2017). This feedback inhibitory mechanism is in line with the sleep promoting functions of galanin neurons in the ventrolateral preoptic area (Kroeger et al., 2018).

RESEARCH CONSEQUENCES

From this review, it is apparent that a lot is still unknown about BFc neuron function. We still do not have an answer for a variety of questions. Some of them will be briefly discussed and summarized.

Perhaps the most acute problem pertains to the inconsistency of reports about the firing behavior of BFc neurons in vivo (Manns et al., 2000; Lee et al., 2005; Duque et al., 2000; Simon et al., 2006). The heterogeneity might stem from regional differences but the anesthesia state and species differences might add to the complexity. Unfortunately, in vitro studies did not help much for clarifying these discrepancies. Instead, the latter studies introduce another level of complexity by finding distinct types of BFc neurons (e.g. Unal et al., 2012). It is currently not known whether the distinct BFc neuron types seen in vitro correspond to different populations in vivo.

Another thought-provoking finding concerns the anatomical organization of BFc neurons: some of these neurons are stacked together forming anatomical clusters while others are relatively more isolated (Zaborszky et al., 2011). It remains to be investigated whether BFc neurons belonging to clusters versus those that do not belong to any cluster exhibit electrophysiological differences and/or functions. Along these lines, the morphological correlates of different electrophysiological populations remain to be investigated.

Despite recent advances in optogenetic methods, there is a lack of studies documenting the neuromodulation of BFc neurons by neuromodulatory hubs such as dopaminergic and noradrenergic systems (Zaborszky et al., 2011). Studies need to test the interactions between BFc neurons and other wake-active neuromodulatory systems for a better understanding of BFc neuron function.

Real time amperometry studies have shown that cholinergic signaling in the cortex constitutes two modes: a phasic mode that can be measured in milliseconds and a tonic mode that occurs at a seconds scale (Sarter et al., 2014). It has been hypothesized that different BFc neuron populations with different firing properties might provide the cortex with acetylcholine at different time scales (Unal et al., 2012). The baseline firing rates of different BFc neuron populations need to be compared in vivo to verify this hypothesis.

CONCLUSIONS AND FUTURE DIRECTIONS

BFc neurons are not only wake-active neurons. These neurons also play vital roles in learning and memory (Hasselmo and Stern, 2018). However, we do not exactly know how these neurons fulfill these functions.

To understand the BFc neuron physiology and function as a whole, single studies focusing on multiple BF regions, using standard protocols are required. These need to be complemented by counting other BFc neurons in the vicinity to analyze whether recorded cells are located within BFc neuron clusters. These two

anatomical features (specific location and being/not being in a cluster) might relate to different electrophysiological properties.

Another anatomical feature that needs to be taken into consideration pertains to the morphology of single BFc neurons that are recorded and electrophysiologically characterized. Finding potential morphological differences in distinct electrophysiological types in vitro could help identifying these neurons in in vivo studies and hence revealing their functional identity. These studies then could be supported by studies that make use of optogenetic activation of BFc neurons.

Last but not the least, different BFc neuron populations might exhibit differences in their gene expression profiles. By identifying such differences, one could incorporate optogenetic silencing/activation methods to reveal the acetylcholine release profile by distinct sets of BFc neurons.

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