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Cholinergic Signaling Dynamics and Cognitive Control of Attention

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Abstract

The central cholinergic system is one of the most important modulator neurotransmitter system implicated in diverse behavioral processes. Activation of the basal forebrain cortical cholinergic input system represents a critical step in cortical information processing. This chapter explores recent developments illustrating cortical cholinergic transmission mediate defined cognitive operations, which is contrary to the traditional view that acetylcholine acts as a slowly acting neuromodulator that influences arousal cortex-wide. Specifically, we review the evidence that phasic cholinergic signaling in the prefrontal cortex is a causal mediator of signal detection. In addition, studies that support the neuromodulatory role of cholinergic inputs in top-down attentional control are summarized. Finally, we review new findings that reveal sex differences and hormonal regulation of the cholinergic-attention system.

Keywords

Acetylcholine; Attention; Muscarinic receptors; Nicotinic receptors; Sex differences

1 Introduction

Cholinergic inputs to the entire cortical mantle originate in the nucleus basalis of Meynert (nBM), substantia innominata (SI), the horizontal nucleus of the diagonal band (HDB), and the preoptic nucleus (collectively termed basal forebrain, BF). The BF corticopetal cholinergic system constitutes the most rostral component of neuromodulatory input systems, and its anatomical organization reflects its ability to orchestrate cortical information processing. Of the many different behavioral and cognitive processes that relate to the central cholinergic system, fundamental aspects of attention are closely linked to the activity of cortical cholinergic inputs (Ballinger et al. 2016; Sarter et al. 2005, 2016). Therefore, there is considerable interest in the dynamics of cortical cholinergic signaling and cholinergic regulation of attentional processes and capacities and developing procholinergic therapies to treat cognitive deficits in psychiatric and neurological disorders.

Historically, the organization of the BF cortical projection system was described as a diffuse and undifferentiated projection system with widespread cortical innervation, which

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corresponds to the notion that acetylcholine (ACh) influences the excitability of neurons cortex-wide to modulate global states of arousal and wakefulness. Earlier studies that focused on slow and regionally nonspecific changes in ACh efflux (volume transmission) supported this view (Bartolini and Pepeu 1967; Descarries 1998; Phillis 1968). However, advancement in electrochemical approaches to monitor neurochemical events at high temporal and spatial resolution in the past decade led to the characterization of phasic ACh release that was linked to specific cognitive events (Howe et al. 2013; Parikh et al. 2007). These developments, along with the refinement of neuroanatomical tools that revealed a highly organized topographic arrangement of cortical target-specific groups of BF cholinergic neurons, challenged previous conceptualization and support modality-/region-specific function of ACh (Lean et al. 2019; Zaborszky et al. 2015, 2018).

Cholinergic signaling is elicited by presynaptic release of ACh that activates two classes of ACh receptors, nicotinic (nAChR) and muscarinic (mAChR), in a spatially and temporally selected fashion due to the constraints imposed by the potent ACh-metabolizing enzyme acetylcholinesterase (AChE). nAChRs are a family of ligand-gated ionotropic receptors that mediate fast synaptic transmission by altering cation channel currents. Neuronal nAChRs are pentameric structures that are formed from a combination of five membrane-spanning units consisting of nine isoforms of α subunits (α2–α10) and three isoforms of β subunits (β2–β4) and arranged either as a heteromeric or homomeric assemblies (Gotti et al. 2009). Within the mammalian cortex, homomeric α7 and heteromeric α4β2 are the most predominant and widely distributed nAChRs. mAChRs are metabotropic receptors that, following activation by ACh, transduce their signaling via heterotrimeric G proteins. The M1 family of mAChRs include M1, M3, and M5 and signals via Gq proteins, while M2 and M4 mAChRs belong to the M2 family that are coupled to Gi proteins (Thiele 2013).

Efforts to develop cholinomimetic drugs as cognition enhancers have largely focused on boosting cholinergic transmission. Although psychopharmacological research to augment cholinergic signaling have generally focused on AChE inhibitors, the procognitive therapeutic efficacy of these drugs in human subjects have remained limited (Pepeu and Giovannini 2009). It is suggested that higher baseline ACh levels, as a result of AChE blockade, would result in generalized activation of cholinergic auto- and hetero-receptors that may uncouple presynaptic and postsynaptic mechanisms and, consequently, produce complex changes in the local cortical networks (Hasselmo and Sarter 2011; Pepeu and Giovannini 2009). Likewise, pharmacological studies that focused on nonselectively modulating mAChRs and nAChRs largely reported complex effects on cognition (Hasselmo and Sarter 2011; Sarter et al. 2009a). This chapter explores recent developments in our understanding of the cholinergic mechanisms of attention. Specifically, the evidence that phasic cholinergic signaling in the prefrontal cortex (PFC) is a causal mediator of signal detection will be discussed. Moreover, studies that support the tonic neuromodulatory role of cholinergic inputs in top-down attentional control, and those that provide insights into the potential cellular substrates that integrate the phasic and neuromodulatory cholinergic signaling modes, will be reviewed. Because sex differences exist in the central cholinergic system, we will also highlight new findings that reveal sex differences in cholinergic-attention system. In conclusion, the framework to develop procholinergic therapies by targeting specific components of cortical cholinergic signaling will be briefly presented.

2 Cortical ACh and Attentional Performance

Substantial evidence from lesion and microdialysis studies supported the hypothesis that cortical cholinergic projections are necessary for performance in tasks that assess a range of attentional functions. A plethora of studies conducted in rodents demonstrated that selective lesions of BF cholinergic neurons and their cortical inputs produced by the immunotoxin 192-IgG saporin impair performance in various tasks of attention. For instance, cortical cholinergic deafferentation of rats trained in an operant sustained attention task (SAT) disrupted animals' ability to detect the signal (correctly respond on signal trials), while sparing response accuracies on non-signal trials (McGaughy et al. 1996, 2000). In a cross-modal divided attention task that requires the processing of a visual and auditory conditioned stimulus, selective cholinergic lesions resulted in a speed-accuracy tradeoff under conditions of modality uncertainty, with longer correct response latencies in bimodal than in unimodal blocks of trials (Botly and De Rosa 2009; Newman and McGaughy 2008; Turchi and Sarter 1997). Additionally, removal of cholinergic inputs from the medial PFC reduced choice accuracies under conditions of increased attentional load and increased perseverative responding in animals performing the five-choice serial reaction time task (Dalley et al. 2004; Maddux et al. 2007). It is noteworthy that lesions of BF cholinergic neurons did not robustly impact performance of subjects trained in tasks that did not explicitly tax attentional processes, illustrating the specificity of cognitive impairments produced by cortical cholinergic deafferentation (Baxter et al. 1995; Frick et al. 2004; Vuckovich et al. 2004).

Studies employing in vivo microdialysis procedures in rats reproducibly demonstrated performance-associated increases in ACh release in the frontal and parietal cortex in operant tasks of attention (Arnold et al. 2002; Dalley et al. 2001; Himmelheber et al. 1997; Kozak et al. 2006; Passetti et al. 2000). More importantly, the levels of ACh release in attentional task-performing animals varied as a function of the demands on attention but did not correlate with levels of attentional performance. Such increases in cortical ACh efflux were not observed in animals performing various operant control procedures that do not explicitly tax attentional processes.

Although this research substantiated the claim made by lesions studies concerning the necessary role of BF cholinergic system in attentional performance, it remained limited in explaining the precise cognitive operations that are supported by cortical cholinergic activity. Microdialysis studies typically required 5–10 min of sample collection to detect ACh concentration in the dialysate using HPLC, which took over tens of trials to generate a single data point. Thus, the low temporal resolution of ACh release data limited the demonstration of specific attention task events or the behavioral/cognitive operations that are responsible for the increases in cortical cholinergic signaling. Consequently, conclusions based on microdialysis data were consistent with the conventional characteristics of ACh as a slowly acting cortex-wide neuromodulator optimizing input processing by regulating arousal states. As noted above, the presence of ubiquitous and highly potent ACh-metabolizing enzyme AChE, and the presence of nAChRs that mediate faster cholinergic signaling, suggests that the functions of forebrain cholinergic system are not sufficiently described by such notions. With the advent of electrochemical approaches and refinement in the design of

enzyme-based microelectrodes, the measurement of cholinergic transmission on a faster time-scale became possible. The evidence generated from research based on these technical breakthroughs, which show rapid (phasic) changes in cholinergic transmission transients in specific behavioral contexts, led to the revision of previous conceptualizations of BF cholinergic system as discussed next.

3 Prefrontal Cholinergic Mechanisms of Signal Detection and Attentional Control

3.1 Phasic ACh Release Mediates Cue Detection

Considerable progress has been made in the development of enzyme-based biosensors to measure electrochemically rapid (on the time-scale of milliseconds to seconds) changes in extracellular choline levels, as a marker for cortical ACh release (Giuliano et al. 2008; Parikh et al. 2004). These approaches allow real-time monitoring of cholinergic signaling on a trial-by-trial basis in tasks of attention and have advanced our understanding of the specific role of phasic cholinergic signaling in signal (cue) detection. *Detection* here implies a cognitive-attentional process that relates to the entry of information concerning the presence of a stimulus (signal or cue) into a processing stream that allows the subject to report the existence of a signal by an arbitrary response established by the experimenter (Posner et al. 1980). This process is distinct from *orientating* that mostly reflects a process of aligning sensory response to the salient cue.

One of the initial studies that employed choline-sensitive biosensors to record cholinergic activity from the medial PFC was conducted in *awake* rats, performing a cued-appetitive response task (Parikh et al. 2007). This study demonstrated phasic cholinergic signals (cholinergic transients) evoked by “detected” cues (visual stimulus) that generated a distinct shift from ongoing behavior (e.g., grooming) toward the monitoring of the reward ports, followed by port approach and reward retrieval in response to reward delivery. The onset of the cholinergic transient was highly correlated with the onset of the behavioral shift. Moreover, prefrontal cholinergic transients were specifically associated with detected cues and did not occur with other task events such as reward delivery and reward retrieval. In trials involving missed cues, where the animal oriented to the cue but failed to initiate any response, cholinergic signals were not observed. Removal of cholinergic inputs to the recording region by locally infusing cholino-immunotoxin 192-IgG saporin, completely abolished cue-evoked phasic cholinergic signals in detected trials confirming that signals originated from cholinergic terminals. Collectively, these findings suggested that transient or phasic increases in prefrontal cholinergic activity mediate cue-evoked cognitive operations in attention-demanding contexts.

Additional experiments indicated that variation in the time interval between cue and reward delivery caused variation of the timing of the peak amplitude of cue-evoked cholinergic signals (Parikh et al. 2007; Parikh and Sarter 2008). This was an important observation as it indicated that cholinergic transients do not merely reflect sensory encoding of the cue. If that was the case, variations of cue-reward intervals should not affect the timing of the cholinergic transients. The variation of the timing of cue-evoked cholinergic transients

indicates that phasic ACh release in the PFC is associated with a cognitive operation (cue detection), the timing of which is a function of cue-reward intervals.

A subsequent study that recorded PFC cholinergic activity in rats performing an operant SAT reported cholinergic transients during "hits," i.e., correct responses on signal trials (Howe et al. 2013). Surprisingly, phasic cholinergic signals were observed only in 40% of hits. The cholinergic transients that were generated during hits were preceded either by correct rejections (correct responses on non-signal trials) or misses (incorrect responses on signal trials). Hits that were not associated with cholinergic transients were those preceded by hits. These findings indicated that phasic cholinergic signals mediate signal detection specifically in situations that involves a shift from monitoring to cue-directed behavior (shift hits). Additional evidence from fMRI studies conducted in humans performing the SAT task illustrated increase BOLD activation in the right rostrolateral/orbital PFC and right BF during shift hits and that this activation was associated with faster reaction times (Howe et al. 2013; Sarter et al. 2016).

Another study that combined optogenetics with electrochemistry tested the hypothesis that cholinergic transients have the capacity to cause signal detection even in the absence of signals (Gritton et al. 2016). Photostimulation of channel rhodopsin-expressed BF cholinergic neurons and prefrontal cholinergic terminals generated optogenetically evoked cholinergic transients and increased hit rates in SAT-performing mice. Moreover, suppression of phasic cholinergic activity by photostimulating halorhodopsin-expressed BF cholinergic neurons resulted in reduced hits without affecting correct rejections. Collectively, these findings indicate that phasic cholinergic signaling, specifically in the PFC, is not only associated exclusively with cue detection but are actually the causal mediators of shift hits (i.e., shifts from monitoring to signal detection). This view aligns with the lesion studies (discussed earlier) that show the detrimental effects of cortical cholinergic deafferentation were linked to detection performance (i.e., hit rates on signal trials and not correct rejections).

3.2 Top-Down Control of Attention and Cholinergic Neuromodulation

The ability to maintain stable task performance in the face of challenges or distractors requires attentional effort (Sarter et al. 2006). Cholinergic neuromodulation of the prefrontal efferent projections is conceptualized to enhance stimulus processing and to suppress the processing of irrelevant stimuli, distractors, or noise in a top-down fashion (Sarter et al. 2005). This hypothesis was supported by previous microdialysis studies that reported sustained increases in cholinergic activity during attentional challenges. For instance, steady increases in ACh efflux in medial PFC of SAT-performing rats were observed when animals moved from non-performing (baseline) stage to the performing (task) stage; however, ACh levels increased further with the presentation of visual distractors despite a reduction in hits (Kozak et al. 2006; St Peters et al. 2011). Human fMRI studies conducted in subjects performing SAT reported comparable increases in right PFC activity from baseline to SAT and then to the distracting condition (Berry et al. 2017; Demeter et al. 2008, 2011). Furthermore, SAT-associated ACh release in the medial PFC was attenuated in sign-tracking rats that show poor attentional control (Paolone et al. 2013).

Extracellular ACh efflux measured using microdialysis reflects a slower (tonic) component of cholinergic signaling that ranges from hundreds of seconds to tens of minutes. Tonic cholinergic activity is proposed to reflect a top-down neuromodulatory role of BF-cholinergic neurons to regulate cortical detection circuitry in an attempt to maintain task performance under conditions of distraction (Sarter and Lustig 2019). Although the dissociation between phasic and neuromodulatory (tonic) components of cholinergic signaling appears to be distinct in terms of cognitive operations; the two modes may interact to support overall attentional performance. This notion is supported by a previous in vivo amperometry study that reported a positive correlation between the magnitude of slower (timescale of minutes) session-related increases in tonic cholinergic activity and the amplitudes of phasic cholinergic signals in animals performing the cued-appetitive response task (Parikh et al. 2007). Given the constraints imposed by AChE on cholinergic signaling, the view that neuromodulatory/tonic cholinergic activity is driven by “volume transmission” is debated (Sarter et al. 2009b). It remains to be seen whether cholinergic neuromodulation is a consequence of sustained activity of BF cholinergic neurons, local presynaptic regulation in the cortical microcircuits, or another population of BF cholinergic neurons that produce tonic discharges (Sarter and Kim 2015; Sarter et al. 2014; Unal et al. 2012).

4 Cellular Regulation of Cholinergic Signaling Modes

4.1 High-Affinity Choline Transporters (CHTs)

Cholinergic terminals recover choline from the synaptic cleft following ACh degradation by AChE, through a hemicholinium-3 (HC-3)-sensitive high-affinity choline transporter (CHT). Because cholinergic synapses rely heavily on choline for ACh production, the capacity to import choline into presynaptic cholinergic compartments via CHTs dictates the rate of ACh synthesis and release (Ferguson and Blakely 2004; Sarter and Parikh 2005). CHT-mediated choline uptake was enhanced in the synaptosomes isolated from the medial PFC of SAT-performing rats; such increases in choline uptake were not observed in animals that completed a behavioral control session (Apparsundaram et al. 2005). The same study also reported attention performance-associated increases in the densities of CHTs on the surface membrane of prefrontal synaptosomes relative to the intracellular pools (outward CHT trafficking). Another study found a decline in the capacity to generate prefrontal cholinergic transients following sustained BF stimulation in CHT heterozygous mice (Parikh et al. 2013). Moreover, these mutants displayed high vulnerability to the effects of visual distractors in SAT and disrupted trafficking of subcellular CHTs. Likewise, a recent fMRI study that involved human subjects expressing a I89V variant of CHT (low CHT capacity) did not find increases in right prefrontal activity in these subjects during increases in attentional demands that is typically seen in normal subjects (Berry et al. 2015). Taken together, these interesting findings point toward an important role of CHT function in regulating presynaptic cholinergic neuromodulation and in sustaining phasic cholinergic signaling under situations that impose increased demands on BF cholinergic neurons, such as top-down attentional control.

4.2 nAChRs

Substantial evidence indicates that the administration of nicotine and nAChR agonists, specifically those that activate α4β2 nAChRs, exert beneficial effects on attention and related cognitive abilities (Allison and Shoaib 2013; Howe et al. 2010; Newhouse et al. 2004; Sarter et al. 2009a; Stolerman et al. 2000; Wilens and Decker 2007). α4β2 nAChRs situated on thalamic glutamatergic projections in the medial PFC are an important component of attention circuitry and that stimulation of these receptors increase glutamatergic activity (Lambe et al. 2003; LucasMeunier et al. 2009). Moreover, neuropharmacological studies employing in vivo amperometry demonstrated that the stimulation of α4β2 nAChRs produces transient increases in glutamate and ACh release in the medial PFC and that thalamocortical glutamatergic terminals are necessary for the generation of cholinergic transients (Parikh et al. 2008, 2010). Moreover, systemic administration of a full α4β2 nAChR agonist S38232 improved attentional performance following the presentation of distractor in rats (Howe et al. 2010). As noted above, attention control requires cholinergic neuromodulation, and it is possible that α4β2 nAChR activation facilitates phasic cholinergic signaling by tonically modulating glutamatergic-cholinergic interactions (Hasselmo and Sarter 2011). Although α7 nAChR agonists have also been reported to augment prefrontal glutamatergic transmission, they did not produce faster cholinergic transients as observed with the stimulation of α4β2 nAChRs (Bortz et al. 2013; Parikh et al. 2010). It is possible that α7 nAChRs recruit other ascending modulators such as monoamines which impact the dynamics of BF cholinergic signaling in a different way resulting in more complex effects on attention.

4.3 mAChRs

Systemic administration of mAChR antagonist scopolamine has consistently been shown to produce attentional impairments indicating that mAChRs may be important for cholinergic mediation of attention (Callahan et al. 1993; Chudasama et al. 2004; Young et al. 2013). However, the beneficial effects of mAChR agonists on cognitive processes have remained complex and could not be reliably demonstrated in clinics presumably due to lack of the availability of specific ligands targeting specific mAChR subtypes. It has been suggested that postsynaptic M1 receptors localized on cortical pyramidal neurons enhance voltage-dependent Ca^{2+} influx and action potential output in response to phasic release of ACh (Dasari et al. 2017). Moreover, a recent study reported that cue-evoked cholinergic transients in the medial PFC of animals performing the Pavlovian cued-approach task triggered theta-gamma coupling, and this synchronization and cue detection was disrupted following M1 receptor blockade (Howe et al. 2017). Thus, M1 receptor activation may regulate phasic ACh-induced prefrontal network synchrony required for cue detection.

5 Sex Differences and the Cholinergic Mediation of Attention

5.1 Neurochemical Sex Differences

The synthesis, release, and postsynaptic effects of many neurotransmitters systems are influenced by biological sex, and the BF corticopetal cholinergic system is no exception. As noted, a critical ACh-producing region within this circuit is the nBM. In rats, although a sex difference is not always observed (Gibbs 1996), there are reports that the nBM of females

has more neurons containing the cholinergic synthetic enzyme, choline acetyltransferase (ChAT), than the nBM of males (Takase et al. 2007, 2009). The sex difference in ChAT neurons may be specific to the nBM, as it does not occur in the HDB (Takase et al. 2009), suggesting that the regions within the BF corticopetal cholinergic system are differentially influenced by sex. An increase in ChAT in the female nBM could facilitate their production of ACh relative to males. Consistent with this idea, the females have higher tonic ACh release than males in the mPFC (Takase et al. 2007, 2009). This sex differences in cortical ACh is observed across the circadian release profile for ACh (Takase et al. 2009). The enhanced tonic cortical ACh release in females may facilitate their top-down attentional control relative to males. However, sex differences in phasic ACh release have not been assessed. Given the greater capacity of females to synthesis of ACh, it is possible that a similar sex difference in phasic cholinergic signals would be detected, but further studies are needed.

Sex differences in ACh production and release likely result from circulating ovarian hormones. Cholinergic neurons in the BF contain estradiol receptors (ER), including ERα and the G-protein coupled ER (Gibbs 1996; Miettinen et al. 2002). Although ER levels in the BF cholinergic neurons are comparable in male and female rats (Gibbs 1996), the higher circulating levels of estradiol in females could preferentially influence their BF. One mechanism by which estradiol could influence cholinergic neurons is via the regulation of ChAT. Estradiol administration to ovariectomized female rats increases ChAT levels in nBM, but not the HDB (Gibbs 1997; Gibbs et al. 1994). In contrast to the role of estradiol, manipulation of testosterone in males does not affect ChAT in the nBM (Nakamura et al. 2002). Collectively, these studies suggest an increased nBM production and release of ACh in females that is driven by estradiol regulation of ChAT.

As noted, ACh exerts its effects through nAChRs and mAChRs. In humans, women have more β2-containing nAChRs and mAChRs in the frontal cortex than men (Cosgrove et al. 2012; Yoshida et al. 2000). These receptors also appear to be regulated by estrogens. Estradiol potentiates the human alpha4beta2 subtype of the nicotinic receptor (Curtis et al. 2002). In rats, mAChR binding is highest in females in the proestrous stage of the estrous cycle, which is the stage when estradiol levels are highest (van Huizen et al. 1994). Additional evidence for estrogenic regulation of cholinergic receptors comes from studies associating the loss of estrogens in menopause with a reduction in nAChRs and mAChRs (Norbury et al. 2007; Tinkler and Voytko 2005). Interestingly, postmenopausal women receiving estrogen replacement therapy have higher mAChR density in the lateral frontal cortex than untreated postmenopausal women (Norbury et al. 2007), indicating that restoring estrogen levels can mitigate against the negative effect of hormone loss on cholinergic receptor levels. When these findings are considered with the aforementioned studies on ACh production and release, it appears that, compared to males, the basal forebrain corticopetal system of females has a greater capacity for producing and responding to ACh, which could improve attention in females.

5.2 Behavioral Sex Differences

Psychiatric disorders with attention dysregulation often occur at different rates in men and women. For example, men are more likely to be diagnosed with ADHD and schizophrenia (Mendrek and Mancini-Marïe 2016; Ramtekkar et al. 2010). These disorders can also present differently in men and women, such that men with schizophrenia, for example, have greater deficits in cognitive processes, including attention (Goldstein et al. 1998; Mendrek and Mancini-Marïe 2016; Zhang et al. 2012). In aging populations, there is evidence that women have higher rates of Alzheimer's disease than men (Gao et al. 1998; Mazure and Swendsen 2016). This sex difference has been attributed to a loss of estradiol in women, and there is some evidence that hormone replacement therapy reduces Alzheimer's disease risk, especially when hormone replacement therapy is initiated within a short period of oophorectomy or natural menopause (Mielke et al. 2014; Rocca et al. 2011; Whitmer et al. 2011).

In healthy populations, there is also evidence for sex differences in certain aspects of attention. For example, women outperform men on a divided attention paradigm and their enhanced capacity to rapidly switch attention is thought to explain their better ability to multitask than men (Seçer and Yılmazoğulları 2016; Stoet et al. 2013). In rodents, females also do better at certain tasks of attention than males. For example, auditory distractors are less disruptive in female than male mice in an interval timing task (Buhusi et al. 2017). However, sex differences in attention may be specific to certain attentional processes because they are not observed in every attention task. For example, male and female rats perform similarly under baseline parameters in task of spatial divided attention (Bayless et al. 2012; Jentsch and Taylor 2003). When the task is made more difficult (e.g., by increasing the intertrial interval, decreasing the visual stimulus), females make more vigilance errors, while males make more errors of inhibitory control (Bayless et al. 2012, Jentsch and Taylor 2003). Similarly, performance on the SAT is comparable between male and female rats, even on the signal trials that require the release of ACh in the mPFC (Bangasser et al. 2017; Cole et al. 2016). These studies indicate that sex differences in attention differ based on the attentional process examined and often do not emerge until tested under challenging conditions.

There are some reports of estradiol regulating attentional processes. On a task of divided attention, a loss of estrogens impaired performance when conditions were challenging and this decrement was rescued by the administration of estradiol (Barnes et al. 2006). In contrast, performance in the sustained attention did not change across the estrous cycle (Cole et al. 2016), and ovariectomy did not impair performance on the task and, surprisingly, prevented a decrease in performance across the session (McGaughy and Sarter 1999). However, if BF cholinergic neurons were damaged with a selective neurotoxin, high levels of estradiol improved aspects of performance on the sustained attention task (McGaughy and Sarter 1999). These data suggest that when task parameters are easy the effects of estradiol on attention are difficult to detect; however, when the system is challenged, estradiol improves attention. In support of this, we challenged male and female rats with the stress neuropeptide, corticotropin-releasing factor (CRF), and assessed their performance on the sustained attention task (Cole et al. 2016). We found a significant dose-dependent

impairment in all aspects of attention that was similar between the sexes. However, when the estrous cycle stage was assessed in females, we found that CRF impaired attention during estrous cycle phases with low levels of ovarian hormones but had little effect during phases with high levels of ovarian hormones (Cole et al. 2016). Functional connectivity analysis on brain networks activated (as measured with cFOS) by CRF revealed that female in the proestrous phase of their cycle that is characterized by high ovarian hormone levels had higher connectivity between the nBM and mPFC than females in the phase of their cycle with low ovarian hormones and males (Wiersielis et al. 2016). This finding indicates that estradiol may promote stress resilience by increasing the coupling of brain regions within the of the BF corticopetal cholinergic system. The mechanism by which this occurs, however, remains to be determined.

In sum, females appear to produce and release more ACh in the BF corticopetal system, and this effect is linked to estradiol. When it comes to behavior, which is more complex and often involves many regions, neurotransmitter, and hormones systems, there tends to be a bias toward females being better than males in certain aspects of attention, but this does not occur for all endpoints tested. When the system is challenged, however, estradiol can help promote resilience to attention deficits. This finding suggests that treatment with estrogens may be a method to improve attention in people diagnosed with psychiatric disorders. In support of this idea, the selective estrogen receptor modulator, raloxifene, improved attention/processing speed for both men and women with schizophrenia (Weickert et al. 2015). More work is needed, but understanding sex differences and hormonal regulation of the BF corticopetal cholinergic system will likely lead to novel therapies to improve cognition in psychiatric patients.

6 Conclusions

The presented evidence in support of the view that cortical cholinergic signaling mediates discrete components of attentional processing challenges the traditional conceptualizations that view ACh as a slow neuromodulator of cortical arousal. The findings that phasic ACh release mediates the detection of signals in attention-demanding contexts have major implications in understanding the role of cholinergic dysfunction in the manifestation of cognitive symptoms of neuropsychiatric disorders and age-related dementias. Dysregulated phasic cholinergic transients could disrupt attentional abilities of patients suffering from schizophrenia and attention-deficit hyperactivity disorder (Sarter and Paolone 2011; Sarter et al. 2012). Abnormalities in the orchestration of phasic cholinergic signaling may precede global and structural decline in cholinergic function and consequently the loss of cholinergic neurons in Alzheimer’s disease (Mesulam 2004).

The development of procholinergic drugs to improve cognitive symptoms of psychiatric and neurological conditions may benefit tremendously by moving away from previous views concerning volume transmission of ACh and not focusing on drugs that produce generalized increase in cholinergic transmission (such as AChE inhibitors). As discussed above, the new evidence from neuropharmacology and behavioral studies indicate that drugs that specifically amplify cholinergic transients via tonic neuromodulation of cholinergic synapses (e.g., $\alpha 4\beta 2$ nAChR agonists) may improve attentional control. Likewise, M1-selective

mAChR agonists may exert beneficial effects on cue detection by enhancing the efficiency of phasic ACh for synchronizing the activity of prefrontal networks. At the presynaptic level, drugs that influence molecular mechanisms to enhance the capacity of cholinergic synapses to sustain phasic cholinergic signaling (e.g., choline transporter-mediated choline uptake mechanisms) may enhance attentional performance. Finally, research on the hormonal regulation of cholinergic transmission is just beginning to answer specific questions concerning sex differences in the cholinergic-attention system. This research will greatly benefit the development of procholinergic drugs for sex-specific treatment of the cognitive symptoms of psychiatric disorders.

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