CHOLINERGIC CIRCUITS AND SIGNALING IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Abstract

Central cholinergic signaling has long been associated with aspects of memory, motivation, and mood, each affected functions in neuropsychiatric disorders such as schizophrenia. In this chapter, we review evidence related to the core hypothesis that dysregulation of central cholinergic signaling contributes to the pathophysiology of schizophrenia. Although central cholinergic circuits are resistant to simplification—particularly when one tries to parse the contributions of various classes of cholinergic receptors to disease related phenomena—the potential role of ACh signaling in Schizophrenia pathophysiology deserves careful consideration for prospective therapeutics. The established role of cholinergic circuits in attentional tuning is considered along with recent work on how the patterning of cholinergic activity may modulate corticostriatal circuits affected in schizophrenia.

I. Introduction

Cholinergic innervation of cortical and striatal brain areas is extensive and diffuse, as are both pre- and postsynaptic targets for acetylcholine (ACh) interaction. Receptors for ACh (AChRs) come in two broad classes—ionotropic (nicotinic) and metabotropic (muscarinic)—each class having multiple subtypes with both opposing and synergistic actions. Activation of these receptors regulates neuronal excitability by interaction with pre- and postsynaptically localized ACh-binding sites. ACh can act as a tonic, diffuse signal, modulating the release of ACh and other transmitters, including dopamine, glutamate, and GABA. Alternatively, ACh can exert its effects via highly localized and directed interactions with neuronal AChRs to increase or decrease neuronal firing.

The complexity of CNS cholinergic circuits and signaling mechanisms produces a system in which origins and end results may be easier to appreciate than intervening steps. It is clear that ACh, released from the cholinergic inputs of the basal forebrain, striatal, and the pontomesencephalic (PM) areas, plays an important role in supporting neurocognitive and motivational functions of the prefrontal cortical, hippocampal, and ventral tegmental projections to the striatum (for reviews see Cragg, 2006; Gotti and Clementi, 2004; chapter by Martin and Freedman, this volume; Mesulam, 2004; Sarter *et al*., 2005; Smythies, 2005; Wonnacott *et al*., 2005). In addition, there is considerable evidence that events which reduce the amount of ACh at cholinergic targets may contribute to functional deficits—including deficits related to schizophrenia (Hyde and Crook, 2001; Sarter *et al*., 2005; chapter by Martin and Freedman, this volume). But considerable confusion sets in when one tries to extract exactly *how* the intervening steps, with activation of muscarinic and/or nicotinic receptors and

consequent changes in downstream circuits, are integrated to elicit the broad spectrum of effects modulated by cholinergic signaling.

Some of the confusion arises from attempts to reconcile the varying "anticholinergic" properties of antipsychotic medications with data on the effects of muscarinic agonists per se. Further confusion arises from the fact that commonly used cholinergic ligands may be less specific in their binding properties than previously thought: indeed, some compounds traditionally considered selective muscarinic antagonists may function as partial agonists or antagonists of other ACh (nicotinic and muscarinic) receptor subtypes. Finally, schemes that overemphasize the role of a particular ACh-signaling pathway to the exclusion of others, rather than viewing the function of cholinergic circuits as the result of the summation of actions of ACh at all of its receptors, may do more to confuse than enlighten. Anatomical and functional data underscore the interaction of cholinergic circuits with other neurotransmitter systems (Smiley *et al.*, 1999). Indeed, interaction of ACh with its full panoply of receptor sites elicits substantive changes in the synaptic transmission of dopamine, glutamate, serotonin, and GABA in a variety of brain regions.

We will first provide a thumbnail sketch of cholinergic circuits and then examine how they are involved in functions relevant to schizophrenia with focus on interactions with dopamine- and glutamate-mediated signaling. We will then review developmental/genetic, pathological, and pharmacological evidence for potential cholinergic contributions to schizophrenia. Although cholinergic signaling may not be the major site of circuit dysregulation underlying the etiology of schizophrenia, more knowledgeable manipulation of cholinergic systems may provide an untapped reservoir of considerable therapeutic potential in the treatment of the positive and negative symptoms of this complex disease.

II. ACh in Brain Regions Implicated in Schizophrenia

Central cholinergic circuits participate in aspects of memory formation, motivational and volitional behaviors, and affect. Each of these functions is altered in neuropsychiatric disorders, including schizophrenia. Cholinergic neurons in the CNS make up for any apparent deficit in numbers by projecting to a broad swath of cerebral cortical mantle, select portions of the temporal lobe, and by their profuse axonal arborizations throughout the corpus striatum. The schematic diagram presented in Fig. 1 attempts to bring some order to the cholinergic chaos by corralling the diverse targets of ACh innervation into a manageable subset of brain regions strongly implicated in schizophrenia. Our focus is represented in primary colors: red for cholinergic neuronal groups and a subset of their projections, and yellow for the chosen cholinoceptive targets—brain regions that have been examined in detail in recent circuit analyses and that will be the focus of this chapter. Obviously this degree of simplification endangers the generality of our considerations—for example, there is little discussion of cholinergic signaling in amygdala, or in cingulate or somatosensory cortex—areas of study that have contributed important progress to our understanding of central cholinergic coding. Such omissions are not intended to infer relative impact on the field, but rather reflect the limits of time, space, and comprehension of the authors.

Overall, there are three major groups of cholinergic neurons and interneurons within the primate brain. Cholinergic inputs to prefrontal cortex and hippocampus arise primarily from the basal forebrain group, which includes the medial septal cholinergic neurons, the nucleus basalis of Meynert (nbM) and the preoptic and diagonal band nuclei (Fig. 1, right). Other contributors to the forebrain ACh groups are neurons within the substantia innominata and ventral pallidum. The relative contribution of cholinergic versus noncholinergic neurons to each of the basal forebrain nuclei ranges from <5% to 90% in human brain, with the nbM as the highest density forebrain cholinergic nucleus (Mesulam *et al*., 1984; reviewed in Hyde and

Crook, 2001). Other major targets of the basal forebrain groups include the amygdala, olfactory bulb, and hypothalamus (Woolf, 1991).

The second major subgroup of ACh-containing neurons (Fig. 1, left), the PM cholinergic neurons, provides input to brainstem aminergic nuclei (e.g., VTA, SN, raphe) as well as to the cerebellum, thalamus, and hypothalamus (Woolf, 1991). In addition, the PM group of neurons project to the basal forebrain cholinergic neurons, thereby coordinating central cholinergic modulation of brainstem, midbrain, and forebrain circuits.

The final major group of cholinergic neurons consists of the ACh interneurons that are intrinsic to the basal ganglia. These intrastriatal neurons modulate the relative impact of multiple glutamatergic and dopaminergic circuits on the medium spiny GABAergic projection neurons of the striatum: our focus will be on the role of cholinergic circuits in the regulation of ventral striatal signaling.

A. Cholinergic Pathways Within the Ventral Striatum

Cholinergic neurons within the striatum are typically large, aspiny neurons that comprise 1–5% of the striatal interneurons, varying somewhat with species and consideration of dorsal versus ventral regions. The extensive arborizations of the striatal cholinergic interneurons throughout the corpus striatum provide a tonic level of ACh release, with the ultimate concentration of extracellular ACh being set (and reset) by the interplay of local ACh release and the activity of the omnipresent acetylcholinesterase (AChE).

Striatal cholinergic neurons are characterized by their tonic activation profile, and periods of relatively low activity (referred to as "pauses") can be associated with salience and prediction of reward (Cragg, 2006; Graybiel *et al.*, 1994). The phasic lulls and peaks of the striatal cholinergic activity, which alters local ACh and choline concentrations, are influenced by corticostriatal projections from hippocampal subicular and prefrontal glutamatergic neurons (Fig. 1, in blue), as well as from amygdala, cingulate, and other cerebral and temporal cortices (not shown). In the rodent, the bulk of the hippocampal projections to the nucleus accumbens arise from ventral rather than dorsal hippocampal areas analogous to the more anterior portions of the primate hippocampus.

Dopaminergic inputs to the ventral striatum arise from the ventral tegmentum (VTA) and substantia nigra (SN), which themselves are recipients of cholinergic projections from PM neurons. Activation of a variety of pre- and postsynaptic dopamine receptors strongly regulates the release of ACh and the excitability of striatal cholinergic interneurons (Maurice *et al.*, 2004; Wang *et al.*, 2006). In addition, local circuits of opiate peptide and GABAergic neurons influence the net levels of striatal cholinergic tone.

Even this, admittedly limited, summary of key regulators of the spatial and temporal profile of ACh-mediated signaling in striatum reveals considerable complexity. Nevertheless, recent progress in dissecting the interaction of cholinergic circuits with dopaminergic and glutamatergic inputs to the striatum inspires considerable hope that we may be approaching a *bona fide* understanding of how ACh works at least in *one* region that is known to effect in schizophrenia and that is particularly high in ACh tone (see below and Cragg, 2006; Calabresi *et al.*, 2000; Wilson, 2006; Wonnacott, 2005 for reviews; Wang *et al.*, 2006).

B. Cholinergic Projections in Prefrontal Cortex and Hippocampus

The principal source of cholinergic input to the PFC and hippocampus is from the basal forebrain nuclei, with particularly strong contributions from the medial septum in rodent and from the nbM in human brain. The primate prefrontal cortex receives a fairly homogeneous cholinergic input with the highest density of cholinergic marker-positive fibers in layers I, II,

and V (Lewis, 1990; Smiley *et al*., 1997). Cholinergic axons within the cerebral cortex of human brain are studded with numerous *en passant* swellings that serial EM reveals as primarily asymmetric type synapses. Close appositions of cholinergic synaptic profiles in cortex (Mesulam, 1999, 2004; Smiley *et al*., 1997) as well as the prevalence of cholinergic marker-positive swellings in the vicinity of pyramidal and nonpyramidal neurons in PFC and hippocampus is consistent with proposed modulatory effects of ACh on both excitatory and inhibitory cortical circuits (Mansvelder *et al*., 2006). Likewise, evidence has accrued that the release of ACh per se is likely subject to cholinergic, as well as dopaminergic, synaptic tuning in both PFC and hippocampus (DeBoer *et al*., 1996; Moore *et al*., 1999).

III. Physiology of ACh Circuits and Signaling in Brain Regions Implicated in Schizophrenia Pathology

A. ACh Receptors in the CNS

When clinicians and patients contemplate the "anticholinergic" side effects of various drugs, they often focus on the diverse and distressing array of peripheral autonomic cholinergic actions, including alterations in gastrointestinal function, nausea, and changes in appetite. In fact, the binding sites with which cholinergic drugs interact in the CNS are just as diverse as those in the periphery and often more accessible than expected, despite the blood–brain barrier. Any careful deliberation on ACh-binding sites in the CNS must include ACh-degradative, synthetic, and transporter proteins, as well as the multimembered muscarinic and nicotinic receptor subtypes (for reviews see Calabresi *et al*., 2000; Cobb and Davies, 2005; Gotti and Clementi, 2004; Mansvelder *et al*., 2006; Newhouse *et al*., 2004; Sarter *et al*., 2005). Pharmacological agents originally identified for their activity as AChE inhibitors (such as physostigmine and galantamine) are now known to act as partial agonists or antagonists of specific subtypes of CNS nicotinic AChRs (nAChRs). The oldest and most established "antimuscarinic" agent, atropine, blocks multiple classes of nAChRs at submicromolar concentrations—well within the clinically relevant and experimentally typical range of doses (Zwart *et al*., 1999). Carbamylcholine is more than a muscarinic agonist—it gates deliciously long openings of nAChRs. Finally, the activation of different types of pre-synaptic nicotinic *and* muscarinic receptors can facilitate or depress the release of ACh itself (see below).

Awareness of the complexities in the number and pharmacodiversity of ACh-binding partners in the CNS is essential to evaluating the past and present literature on ACh circuits and signaling. Humbling though this may be, we are actually well positioned to do so: the last 20 years have yielded impressive advances in understanding the differential regulation, expression, targeting, and function of the many muscarinic (at least 5 genes, so far) and nicotinic (11 subunit genes) receptors (see below). With this knowledge in hand, we need to reassess the effects of the pharmaceuticals we have and work toward the development of agents that more selectively manipulate the synthesis, release, and binding(s) of ACh.

A quick primer then, on the most important of ACh-binding sites, from information largely extracted from the following reviews: Calabresi *et al*. (2000); Gotti and Clementi (2004); Laviolette and van der Kooy (2004); MacDermott *et al*. (1999); Mansvelder *et al*. (2006); Sarter and Parikh (2005); Smythies (2005); Wonnacot *et al*. (2005).

   1. *Choline acetyltransferase* (*ChAT*): This enzyme is responsible for ACh synthesis. The regulation of ChAT gene expression in the CNS is thought to be coordinated with that of vAChT, by virtue of a common "cholinergic locus" promoter. However, the distribution of these two proteins between somatodendritic and axonal domains may be regulated independently.

2. *ACh esterase* (*AChE*): This binds ACh with micromolar affinity and is considered the principal degradative activity for ACh. AChE is one of the fastest turnover rate enzymes identified and is located primarily at intraneuronal and extracellular sites. Despite its preeminence as "the AChE," recent work deleting AChE-encoding genes revealed that butyrylcholinesterase (BuChE) activity, which is associated with glial cells rather than neurons, can maintain grossly normal ACh balance. So BuChE is another ACh-binding partner to bear in mind.

3. *The vesicular ACh transporter* (*vAChT*): This binds ACh with submicromolar affinity and translocates it into vesicular compartments within cholinergic neurons.

4. *Muscarinic* (*metabotropic*) *AChRs*: At least five genes are identified to date (M1–M5); M1, M2, and M4 subtypes predominate in the CNS. These ACh-binding proteins are coupled to a variety of G-proteins resulting in the activation or inhibition of an even wider variety of enzymatic and ion channel targets. Note that in the CNS, only a subset of the muscarinic-binding sites are postsynaptic; other subtypes of muscarinic receptors are targeted to axonal/presynaptic sites where they modulate the release of glutamate, dopamine, and ACh, among other key players.

5. *Nicotinic* (*ionotropic*) *AChRs*: Twelve subunit genes (α2–α10; β2–β4) encode a group of proteins that are faintly related to—and pharmacologically very distinct from—the renowned muscle-type nicotinic receptors. Drugs that interact with subtypes of neuronal nicotinic receptors (e.g., nicotine, hexamethonium) barely touch the muscle receptor and vice versa. Also important to note is that in the CNS, nAChRs, just like muscarinic receptors, are targeted to *pre-* as well as postsynaptic locations. In fact, the role of presynaptic nicotinic receptors as modulators of dopamine, glutamate, GABA, serotonin, and ACh release is so prevalent in the CNS that their contribution as postsynaptic receptors is often overlooked (but see Frazier *et al*., 1998; Jones and Yakel, 1997)!

In sum, a circumspect evaluation of how the dysregulation of cholinergic circuits may be involved in the pathophysiology requires recognition that ACh targets are many, perhaps not as pharmacologically distinct as previously considered and at pre-, post-, and perisynaptic locations. Viewing the function of cholinergic circuits as the result of the summation of actions of ACh at all of its receptors, although initially daunting, may resolve some apparent conflicts in the literature and guide the way to new therapeutic approaches (for reviews see Calabresi *et al*., 2000; Gotti and Clementi, 2004; Laviolette and van der Kooy, 2004; MacDermott *et al*., 1999; Mansvelder *et al*., 2006; Sarter and Parikh, 2005; Sarter *et al*., 2005; Smythies, 2005; Wonnacot *et al*., 2005).

B. Physiology of Ach Circuits in Striatum

The striatum is established stomping grounds for fans of central cholinergic circuits and ACh signaling. Although the numbers of cholinergic neurons in the striatum are small, they are the foremost, if not the exclusive, source of the high-pack cholinergic inputs in mammalian striatum. As discussed above, striatal cholinergic neurons are characterized by their large size, aspiny appearance, and tonic activation profile (hence the names ASpN and TANS neurons; Fig. 2). Changes in the activity profile of striatal TANS, referred to as "pauses," are thought to arise in part from the slowing of autonomous pacemaker activity and in part to local changes in dopamine, glutamate, and GABA signaling (Cragg, 2006;Maurice *et al*., 2004;Wang *et al*., 2006). The association between changes in striatal cholinergic "tone" and salience/reward prediction has continued to stoke the fire of physiologists' interests in the workings of striatal ACh circuits (see Cragg, 2006 for review; Apicella, 2002;Maurice *et al*., 2004;Wang *et al*., 2006 for recent highlights).

Perhaps the best studied, although still mechanistically mysterious, role of cholinergic circuits in striatum is in their reciprocal interactions with dopaminergic inputs from the VTA and SN. Recent studies add new dimensions to prior evidence that ACh acts as a key regulator of striatal output by influencing the activity of GABAergic medium spiny neurons (MSpNs, Fig. 2). The newest twist is that ACh is likely to exert its modulatory control on striatal activity through interaction with *both* pre- and postsynaptic, nicotinic *and* muscarinic receptors (Fig. 2). Presynaptic nicotinic receptors have long been implicated in the regulation of striatal dopamine release, with reports identifying some of the nAChR subtypes involved in aspects of nicotine addiction in staggering detail (for review see Wonnacott *et al*., 2005;Tapper *et al*., 2004 for recent highlights). The vague term "regulation" was intentionally employed because one of the points of controversy has been whether dopamine release in striatum is enhanced or depressed by nicotine. It turns out that the answer may be both, depending on the frequency of firing of the dopamine neurons (see Cragg, 2006 for review; Partridge *et al*., 2002;Rice and Cragg, 2004;Zhang and Sulzer, 2004;Zhou *et al*., 2001). The effects of dopamine receptor agonists on modulating the release of ACh in striatum (as well as in PFC and in hippocampus, see below) are also well established (DeBoer *et al*., 1996). But new results reveal that depending on the type and location of the dopaminergic and muscarinic receptors activated, the net effect may be to stably enhance or depress the activity of the GABAergic MSpNs (Cragg, 2006;Wang *et al*., 2006;Wilson, 2006;). Indeed, the potential for mutual tuning of TANS and DANS seems more than flexible enough to account for the differences in valence and timing of all of the synaptic changes observed in striatum (Calabresi *et al*., 2000;Cragg, 2006;Maurice *et al*., 2004;Wang *et al*., 2006).

C. Physiology of Ach Circuits in PFC and Hippocampus

The role of cholinergic signaling in aspects of memory and cognition are typically attributed to the broad spectrum of effects that ACh elicits in altering the excitability of prefrontal cortical and hippocampal circuits (for reviews see Albuquerque *et al*., 1996; Buzsaki, 2002; Levin *et al*., 2006; Mansvelder *et al*., 2006; Newhouse *et al*., 2004; Picciotto, 2003; Role and Berg, 1996; Sacco *et al*., 2004; Sarter *et al*., 2005; Smythies, 2005; Wonnacott *et al*., 2005). Analysis of the pros and cons of the many theories on *how* ACh actually does what it does to regulate synaptic efficacy in these regions, as with striatum, is best served by considering the potential interaction of ACh with each of its five major sets of binding partners: ChAT, AChE, VAChT, muscarinic, and nAChRs (see discussion above).

ACh transmission in cortex and hippocampus likely involves both localized release and tonic or "volume" transmission (Cobb and Davies, 2005; Vizi and Kiss, 1998). Activation of presynaptic ACh receptors modulates the release of glutamate, ACh, and dopamine in PFC and hippocampus (Colgin *et al*., 2003; Laplante *et al*., 2004; Lucas-Meunier *et al*., 2003), enhancing or depressing transmission depending on the flavor(s) of AChRs expressed (Mansvelder *et al*., 2006; Sarter and Parikh, 2005; Wonnacott *et al*., 2005). Postsynaptic mAChRs and nAChRs have also been implicated in the modulation of PFC and hippocampal circuits (Cobb and Davies, 2005; Frazier *et al*., 1998; Ji *et al*., 2001; Jones and Yakel, 1997).

Perhaps the most important (albeit still controversial in detail) role of ACh circuits in cortex and in hippocampus is in the regulation of theta rhythm oscillatory activity (Buzsaki, 2002; Calabresi *et al*., 2000; Cobb and Davies, 2005; Hasselmo, 2005; Lee *et al*., 2005). Theta-frequency band oscillations constitute a prominent network pattern in all mammals, including humans. Theta activity has been proposed to underlie everything from temporal cooperativity of cortical and subcortical networks to coordinate modifications of synaptic connections within cortex and hippocampus per se (Buzsaki, 2002; Calabresi *et al*., 2000; Cobb and Davies, 2005; Hasselmo, 2005). In any case, there is no doubt that cholinergic circuits, specifically the septal cholinergic projections, play an essential role in theta oscillations, as selective lesion of

the ACh synthesizing neurons in the medial septal/diagonal band nuclei abolishes hippocampal theta. Discrepancies arise in interpretation of studies that manipulate ACh by different pharmacological means—that is, M1-AChR versus AChE antagonists—which imply that other types of muscarinic and/or nicotinic AChRs may be involved (Buzsaki, 2002; Ji *et al.*, 2001).

IV. Developmental and Genetic Deficits in Schizophrenia That May Influence Function and Assembly of Cholinergic Systems

Schizophrenia is widely viewed as a neurodevelopmental disease, resulting from a combination of environmental challenges acting on susceptible genotypes. Significant progress has been made at identifying both relevant environmental and genetic risk factors (Bresnahan *et al.*, 2005; Harrison and Weinberger, 2005), although we have yet to make progress at understanding how these factors interact to dysregulate relevant circuits in the developing brain. The vertebrate forebrain contains relatively few cholinergic neurons, yet this population exerts widespread modulatory control over essentially all striatal–cortical networks.

Experimental studies have shown that during development, the cholinergic system is especially sensitive to environmental insults (e.g., ethanol, lead, organophosphates, tobacco smoke; Eriksson *et al.*, 2001; Reddy *et al.*, 2003; Robinson, 2002; Thomas *et al.*, 2000). These and other insults would certainly have the potential to interact with genetic vulnerabilities affecting brain development to produce deficits which could contribute to disease states.

A. Development of Cholinergic Systems

Forebrain cholinergic neurons arise early in telencephalic development (~E10 in mouse which approximately corresponds to gestational day 40 in humans; Clancy *et al.*, 2001) in the medial ganglionic eminence, a ventricular/subventricular neurogenic zone that appears as a thickening along the ventral/medial wall of the ventricle (Brady *et al.*, 1989; Furusho, 2006; Marin *et al.*, 2000; Olsson *et al.*, 1998; Semba *et al.*, 1988). Presumptive forebrain projection cholinergic neurons migrate from the MGE (and possibly from the anterior entopeduncular/preoptic area) radially to take up locations in basal forebrain nuclei (medial septum, magnocellular nucleus, diagonal band of Broca), whereas the striatal cholinergic interneurons migrate tangentially from the MGE, occupying dispersed sites throughout the striatal plate. Subsequent to this early birth and migration from the MGE, 1–2 weeks pass before these neurons undergo maturation into cholinergic neurons (Aznavour *et al.*, 2005; Berger-Sweeney, 2003; Mechawar and Descarries, 2001). This delay allows time for other populations of predominantly GABAergic neurons to emerge from the MGE and LGE and occupy their appropriate positions throughout the striatum and cortex for radial population of the neocortex with pyramidal cells and for the proper targeting of axons from the dorsal thalamus to project through the striatal region to innervate cortical structures (Flames *et al.*, 2004; Lopez-Bendito *et al.*, 2006; van Vulpen and van der Kooy, 1998). Some investigators propose that during this period the presumptive cholinergic neurons provide instructive signals that guide the targeting and differentiation of later born striatal populations (Berger-Sweeney, 2003; Hohmann, 2003; Hohmann and Berger-Sweeney, 1998).

During the first two postnatal weeks, the cholinergic interneurons elaborate robust networks of axons locally within the striatum, whereas the forebrain cholinergic neurons elaborate a wide array of axonal projections that target all neocortical regions (prefrontal, sensory, and motor) and the hippocampal formation. As a result these two relatively small populations of cholinergic neurons maximize their ability to interact with striatal–cortical networks. It is likely that the delay between the migration of newly formed cholinergic neurons from neurogenic zones and the elaboration of axonal projections plays a critical role in properly controlling the final wiring of the forebrain cholinergic system.

A number of recent studies using molecular genetic approaches in mice are beginning to clarify the developmental processes that determine the specification of forebrain cholinergic neurons. In particular, the basics of a cholinergic transcription factor code are emerging. A variety of experimental approaches has demonstrated that expression of several transcription factors is important (Mash 1, Olig2, Lmx7, Lmx8) or essential (Nkx2.1) for generating forebrain cholinergic neurons (Bachy and Retaux, 2006; Furusho *et al.*, 2006; Marin *et al.*, 2000; Mori *et al.*, 2004; Zhao *et al.*, 2003). Thus, the combined expression of these factors, and their target genes, probably accounts for much of the intrinsic identity of the cholinergic phenotype. However, these studies have not yet distinguished between factors that determine how a newborn cholinergic neuron migrates from the MGE (radially into basal septal regions or tangentially into the striatum), or whether an individual cholinergic neuron will elaborate a spatially restricted axonal network, as is the case of the striatal interneurons, or a broadly targeted set of cortical projections.

B. Potential Role of Neuregulin 1

Neuregulin 1–ErbB signaling plays multiple critical roles in proper development of the neocortex, guiding both the tangential migration of MGE-derived GABAergic interneurons (Flames *et al.*, 2004) and proper navigation of axonal projections from the dorsal thalamus into the cortex (Lopez-Bendito *et al.*, 2006). Whether neuregulin also guides the migration and/or axon projections of forebrain cholinergic neurons is not known. We have seen apparent decreases in the numbers of specific populations of forebrain interneurons in adult mice that are heterozygous for an isoform specific, targeted mutation in the neuregulin 1 gene (Wolpowitz *et al.*, 2000; Johnson, Talmage, and Role, Unpublished data).

Maturation and maintenance of cholinergic neurons depends on a number of extracellular signaling molecules. Of particular relevance to our discussion of cholinergic signaling and schizophrenia are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and cortical steroids. NGF, BDNF, and glucocorticoids regulate the expression of ChAT, enhance the connectivity of, and promote the survival of cholinergic neurons (Fagan *et al.*, 1997; Grosse *et al.*, 2005; Guijarro *et al.*, 2006; Johnston *et al.*, 1987; Mobley *et al.*, 1986; Phillips *et al.*, 2004; Sofroniew *et al.*, 2001; Takahashi, 1998; Takahashi and Goh, 1998; Ward and Hagg, 2000). Reports have demonstrated altered regulation of NGF (Parikh *et al.*, 2003), BDNF (Weickert *et al.*, 2003, 2005), and the HPA axis (Corcoran *et al.*, 2001, 2003) in schizophrenics. Whether these changes alter corticostriatal cholinergic tone remains to be seen.

Beyond general effects on synaptic structures, there is no clear evidence linking the products of identified schizophrenia susceptibility genes with the cholinergic system, with the notable exception of the neuregulin 1 gene. Neuregulin 1 has been linked to schizophrenia in multiple populations, and disease-associated changes in the relative expression of different neuregulin 1 isoforms is seen in the DFPLC and hippocampus. Neuregulin 1 isoforms play important roles in neurodevelopment, in particular in the patterning of the neocortex (Flames *et al.*, 2004; Lopez-Bendito *et al.*, 2006). At present, these latter roles for neuregulin 1 have focused on tangential migration of cortical interneurons and axonal projections from the dorsal thalamus to the neocortex. Given the relative spatial and temporal parallels between these events (GABAergic interneurons originate in the MGE during an overlapping time frame with the striatal cholinergic interneurons) and the reported decreases in the numbers of ventral striatal cholinergic inter-neurons in postmortem tissue from schizophrenics, it is important that studies of the role of neuregulin 1 in forebrain development be extended to the cholinergic system as well.

A more direct association between neuregulin 1 and cholinergic signaling exists at the level of the expression of the nAChRs. Two families of neuregulin 1 isoforms were identified originally by virtue of their ability to regulate the expression of nAChRs at peripheral synapses (Falls *et*

al., 1993; Yang *et al*., 1998). Subsequently, a number of investigators have demonstrated that neuregulin also can increase the synaptic expression of α7-containing nAChRs at central synapses (Kawai *et al*., 2002; Liu *et al*., 2001), and our laboratories have extended this story by demonstrating that neuregulin 1 signaling also regulates presynaptic expression and targeting of the α7 nAChRs (Role and Talmage, unpublished). These latter studies are particularly intriguing in light of the well-documented deficits in α7 nAChRs in schizophrenics, the association of this deficit with defects in P50 measures of auditory gating in schizophrenics and their first degree relatives, and the association of α7 subunit gene promoter polymorphisms with these deficits (see chapter by Martin and Freedman, this volume; Leonard *et al*., 1996, 2002).

V. Clinical and Preclinical Evidence for Deficits in Components of Brain Cholinergic Systems in Schizophrenia

There are numerous examples of deficits in components of brain cholinergic systems that have been linked with schizophrenia. They range from abnormal expression of receptors of various subtypes through decreases in cholinergic neurons in key areas.

A. Deficits in Components of Muscarinic Cholinergic Transmission

Several studies give evidence of alteration of muscarinic ACh receptors in the brains of schizophrenics. The majority of evidence in this realm points to decrements in binding suggestive of a decrease in available m1 muscarinic-binding sites in prefrontal cortex and hippocampus.

Using [(123)I]IQNB SPECT, one group found decreased muscarinic receptor availability in unmedicated patients with schizophrenia as compared to controls in a variety of cortical and subcortical brain regions (Raedler *et al*., 2003). Another group used GTP-γS binding to distinguish M2 and M3 muscarinic receptors and found no change in postmortem cortex from patients with schizophrenia as compared to controls, while finding a reduction in M1 (Scarr *et al*., 2006). Other groups have found decreased pirenzapine binding in the hippocampus in brains of patients with schizophrenia (Crook *et al*., 2000) and decreased M1 receptor mRNA in dorsolateral prefrontal cortex (Dean *et al*., 2002) but not caudate nucleus (Dean *et al*., 2000).

At the level of genetic findings, there is evidence for linkage of an M1 polymorphism to decreased performance on the Wisonsin Card Sort Test (Liao *et al*., 2003). In addition, there is evidence that an M5 polymorphism confers susceptibility to schizophrenia. Interestingly, the M5 variant seems to confer risk only in combination with a nicotinic α7 polymorphism (De Luca *et al*., 2004).

Finally, it has been reported that circulating antibodies to the M1 receptor can be identified in the serum of some schizophrenic patients. These antibodies displace tritiated pirenzapine and have agonist-like properties at the M1 receptor in *in vitro* assays (Borda *et al*., 2002).

B. Deficits in Components of Nicotinic Cholinergic Transmission

There is also ample evidence of alterations of nAChRs in the brains of patients with schizophrenia. The most notable set of findings pertains to decrements in α7-containing nAChRs and their function in sensory gating. These studies are dealt with in detail in the subsequent chapter by Martin and Freedman, this volume.

Apart from the well-defined case of α7-containing nicotinic receptors, more global changes in nicotinic cholinergic receptors have been observed as well. One group observed decreased

high-affinity nicotine and epibatidine binding in postmortem brains from patients with schizophrenia as compared to controls (Breese *et al*., 2000). The differences were seen in hippocampus, cortex, and caudate in the subgroup of patients versus controls who smoked. The same group reported increases in receptor sites in nicotine and haldol treated rats (Breese *et al*., 2000). However, another group found elevation of nicotine binding in the striatum of patients with schizophrenia (Court *et al*., 2000) and minimal changes in α-bungarotoxin binding in the thalamus (Court *et al*., 1999).

C. Deficits in Cholinergic Innervation

Besides decrements in receptors for ACh, one group has observed a reduction in numbers of cholinergic interneurons in the ventral striatum (Holt *et al*., 1999, 2005), but not in other striatal regions. However, cortical cholinesterase and ChAT activity is not reduced in the brains of patients with schizophrenia (Haroutunian *et al*., 1994).

D. Summary

There are numerous findings of abnormalities in the expression or distribution of many components of cholinergic systems in the brains of patients with schizophrenia, the bulk of which would be expected to lead to decrements in cholinergic neurotransmission. It is unclear whether all of these are primary deficits or in some cases downstream effects of other lesions. At least some cholinergic deficits may have to interact with deficits in other systems in order to confer disease vulnerability. However, despite these uncertainties, the preponderance of evidence points toward possible roles for abnormalities in cholinergic systems participating in the pathophysiology of schizophrenia.

VI. Evidence for Cholinergic Contributions to Schizophrenia Pathophysiology from Clinical and Preclinical Psychopharmacology

Correlation of the efficacy of medications used to treat target symptoms of schizophrenia with effects of those medications on cholinergic systems has been another way in which investigators have attempted to infer potential roles for cholinergic systems in the pathophysiology of schizophrenia. The complex receptor-binding properties of antipsychotic medications and complex relationships of target symptoms and medication side effects have made it difficult to make such inferences in a clear and convincing way. That said, there seems to be ample evidence that well-chosen cholinergic targets have potential to be therapeutic targets.

A. ACh Release, Muscarinic Blockade, Partial Agonists, and "Atypicality"

Preclinical studies have demonstrated that many antipsychotic medications cause the release of ACh in cortical (Ichikawa *et al*., 2002; Li *et al*., 2005) and hippocampal regions (Johnson *et al*., 2005; Shirazi-Southall *et al*., 2002). While a broad range of antipsychotic medications have been shown to release cortical and hippocampal ACh, olanzapine and clozapine have been shown to be especially potent in this regard. Interestingly, these are the two antipsychotic medications which seem to have greater efficacy against a broader range of symptoms than other antipsychotic medications (Kane *et al*., 1988, 2001; Lieberman *et al*., 2003, 2005).

To some extent, antipsychotic-induced release of cortical ACh correlates with M2 binding affinity; antipsychotic medications with less M2 binding tend to be less potent inducers of cortical ACh release (Johnson *et al*., 2005). Observations such as these combined with the observation that both clozapine and olanzapine bind muscarinic receptors with high affinity have led to the idea that anticholinergic properties of antipsychotic medications might be responsible for ACh release, and further might be correlated with "atypicality." This scenario

is plausible in that muscarinic receptors can serve as inhibitory presynaptic auto-receptors, providing a potential mechanism by which their blockade could augment ACh release.

However, olanzapine and clozapine may be only weakly antimuscarinic at the level of clinical symptoms, with fewer anticholinergic side effects than expected based on their potent *in vitro* displacement of muscarinic ligands (Bymaster *et al*., 1996). This discrepancy is likely due both to subtype selectivity at muscarinic sites, and to partial agonist activity at M4 and M2 receptors (Bymaster *et al*., 2003; Michal *et al*., 1999).

Interestingly, clozapine has cognition impairing properties in mice, but the effect is complex, in that clozapine reduces scopolamine-induced impairment while its direct effects on cognition are reversed by cholinesterase inhibitors. This pattern of reduction of antagonist effects and reversal by treatments that increase the endogenous ligand is highly suggestive of partial agonist effects (Ninan and Kulkarni, 1996) or of interaction of ACh with other types of muscarinic and/or nicotinic receptors (see above). Of note, at least two other compounds, xanomeline (reviewed in Mirza *et al*., 2003) and PTAC (Bymaster *et al*., 1999), show antipsychotic-like activity in animal models and are also partial agonists at M4 and M2 receptors.

A further wrinkle in this data is introduced by the fact that both clozapine and olanzapine still release cortical and hippocampal ACh in mice lacking M2 and M4 receptors (Bymaster *et al*., 2003). As such, neither blockade nor partial agonism at these sites appears to be required for ACh release. In view of recent studies implicating both presynaptic nicotinic and dopamine receptors in the modulation of ACh release, the potential contribution of these pathways to the effects of clozapine and olanzapine should, perhaps, be considered.

B. Both Procholinergic and Anticholinergic Compounds May Ameliorate or Worsen Different Symptom Domains

Adding further to confusion about the role of cholinergic transmission in schizophrenia, muscarinic agonists and antagonists exert opposing effects on various schizophrenia symptom clusters. There has been extensive interest in this area because of the use of medications with "anticholinergic" properties as antipsychotics (e.g., chlorpromazine, perphenazine) and because of the use of medications such as benztropine and biperiden to counter the parkinsonian side effects of traditional neuroleptic antipsychotics. For some time, the prevailing opinion seems to have been that anticholinergic effects were fairly neutral in relation to symptoms of schizophrenia, but closer examination has revealed a more complicated picture.

Several studies showed some increase in positive symptoms (hallucinations and delusions) when anticholinergic medications were added to neuroleptics. In a placebo-controlled trial, procyclidine or placebo was added to flupenthixol in a group of 36 patients, with the subsequent finding that those receiving procyclidine had more positive symptoms than those receiving placebo (Johnstone *et al*., 1983). Another study compared symptoms in 47 patients receiving neuroleptics during periods with and without treatment with benztropine or trihexyphenidyl. Again, the anticholinergic medication was associated with an increase in positive symptoms (Singh *et al*., 1987). A study showed that biperiden increased positive symptoms in a small group of schizophrenic patients when added during a medication free period, strengthening the case that the symptomatic worsening is a direct anticholinergic effect rather than one that depends on interaction with the effects of other medications (Tandon *et al*., 1991).

Anticholinergic compounds such as benztropine have been shown to cause memory impairment (Brebion *et al*., 2004; Tune *et al*., 1982). In one small study, higher serum anticholinergic levels correlated with worsened recall but improved reaction time (Strauss *et al*., 1990). It is possible that improvements in reaction time represent an anti-parkinsonian

effect as all patients in the study were taking antipsychotic medications. In another study, single injections of benztropine or glycopyrrolate impaired free recall (McEvoy and Freter, 1989). Overall, it appears likely that anticholinergic medications could worsen some cognitive deficits in schizophrenia.

At the same time, there is a small body of evidence showing that anticholinergic may decrease some negative symptoms in schizophrenia. This provides an instance in which the domain of cognitive symptoms and the domain of negative symptoms can be separated from one another in part based on how they are affected by pharmacological treatment.

In one study, treatment of a small number of patients with trihexyphenidyl resulted in decreases in affective flattening, avolition, and anhedonia/asociality (Tandon *et al.*, 1992). In another study by the same group, biperiden also reduced negative symptoms (while increasing positive symptoms; Tandon *et al.*, 1991). Abuse of trihexyphenidyl and benztropine has at times been cited as "self-medication" of negative symptoms by patients with schizophrenia, and indeed in one study those who abused these medications tended to have higher Brief Psychiatric Rating Scale (BPRS) scores and more negative symptoms than those who did not abuse anticholinergic medications (Zemishlany *et al.*, 1996).

One might speculate that actions of anticholinergic medications against negative symptoms reflect activity in psychomotor circuits that are parallel in some way to the motor circuits in which anticholinergic medications oppose the parkinsonian actions of neuroleptics.

Conversely, muscarinic *agonists* have been proposed to have antipsychotic activity and may have potential effects against positive symptoms with particular attention paid to the compound xanomeline (reviewed in Bymaster *et al.*, 2002, 2003).

Recent findings on the function of muscarinic receptors in the striatum may shed some light on these apparent paradoxes. The recent paper by Wang and coworkers (also discussed in Section III.B of this chapter) shows that D2 dopamine receptors serve to inactivate striatal cholinergic interneurons which signal to M1 muscarinic receptors on MSpNs. In essence, muscarinic stimulation and blockade of dopamine are functional equivalents in this circuit. The muscarinic receptors reduce intracellular calcium in the MSpNs, which in turn reduces the production of endocannabinoids, reducing depolarization induced suppression and long-term depression of neurotransmission. In summary, cholinergic activation in this circuit results in more activity of MSpNs in the indirect pathway—and subsequently less release of inhibition of the corticostriatal pathways that may convert drives and feelings into actions and perceptions. One might predict that this action would reduce positive symptoms in schizophrenia in a manner analogous to that of D2 blockade by neuroleptics, but one might also predict that in some components of these pathways, the same set of actions could result in an increase in negative symptoms (Wang *et al.*, 2006).

While far from clear, the body of evidence on effects of muscarinic agonists and antagonists in schizophrenia, and on the cholinergic binding properties of antipsychotic medications seems to point to a complex role for cholinergic transmission in different domains of psychopathology with loci of action in the brain likely to depend on the specific symptom domain examined. A challenge to neuropyschopharmacologists will be to find ways to balance and dissociate beneficial and harmful effects of blocking and enhancing cholinergic transmission at muscarinic receptors.

C. Nicotine Ameliorates a Wide Range of Deficits Seen in Schizophrenia

A large part of the pharmacological evidence pointing to potential cholinergic roles in schizophrenia pathophysiology concerns salutary effects of nicotine in patients with

schizophrenia. Nicotine affects a wide range of symptom domains and neuropsychological findings. We will give a broad sampling of the data here, and refer the reader to the subsequent chapter by Martin and Freedman, this volume, for an in-depth review of data on nicotinic receptors and the processing of sensory information in schizophrenia.

Nicotine has been shown to improve abnormalities in smooth pursuit eye movement and saccades during visual tracking (Avila *et al*., 2003; Depatie *et al*., 2002; Larrison-Faucher *et al*., 2004; Sherr *et al*., 2002). The improvement in saccades was independent of the smoking status of the patients, thus addressing the possibility that nicotine's effect resulted directly from the elevated incidence of smoking by people with schizophrenia. Nicotine also improved sustained attention in these visual tasks (Avila *et al*., 2003; Depatie *et al*., 2002). The effects of nicotine on performance of visual tracking and tasks of visual attention may involve hippocampus and cingulate gyrus (Levin *et al*., 2006; Newhouse *et al*., 2004; Tanabe *et al*., 2006).

In another domain, nicotine improved performance of tasks involving working memory in schizophrenic subjects, enhancing task-related activation of thalamus and anterior cingulated cortex as seen on fMRI (Jacobsen *et al*., 2004).

Nicotine has also been shown to reverse haloperidol-induced impairments in reaction time and working memory (Levin *et al*., 1996). Nicotine nasal spray improved delayed recognition and spatial working memory in schizophrenic patients (Myers *et al*., 2004; Smith *et al*., 2006). Interestingly, nicotine may actually impair working memory in otherwise healthy smokers (Park *et al*., 2000) suggesting an inherent difference in nicotine responses in the brains of persons with schizophrenia (discussed in Mansvelder *et al*., 2006; Newhouse *et al*., 2004).

While numerous studies show beneficial effects of administered nicotine in schizophrenia, the reverse is not true, that is to say, nicotine withdrawal did not increase positive symptoms in a group of patients with schizophrenia who quit smoking. Increases in negative symptoms were modest and transient (Dalack *et al*., 1999). In considering these results, it may be important to take into account that the frequent high peaks of nicotine delivered by smoking may not be of sustained therapeutic benefit as compared to other systems of delivery.

Finally, the fairly extensive data on sensory processing and nicotine is perhaps the best pharmacological evidence for a role of cholinergic systems in schizophrenia. It is made stronger by the linkage of a polymorphism in the α7 nicotinic receptor subunit gene to sensory gating deficits in patients with schizophrenia and their relatives (Freedman *et al*., 2003; see chapter by Martin and Freedman, this volume). This topic is reviewed in detail in the subsequent chapter by Martin and Freedman, this volume. Overall, and in contrast to the data on muscarinic AChRs, evidence to date strongly supports the notion that treatments that interact with nAChRs have almost uniformly ameliorative effects on symptoms of schizophrenia.

D. Despite Clear Effects of Other Cholinergic Compounds, Cholinesterase Inhibitors Are Not Proven Adjuncts in the Treatment of Schizophrenia

Further pharmacological evidence concerning cholinergic participation in the pathophysiology of schizophrenia comes from studies in which patients were treated with medications from the family of AChE inhibitors which were initially developed to treat Alzheimer's disease (Coyle and Kershaw, 2001; Crismon, 1994; Dooley and Lamb, 2000; Jann, 2000). The effects of these medications in patients with schizophrenia are equivocal at best.

There are several case reports describing improvement in negative and cognitive symptoms of individual patients with cholinesterase inhibitors (Rosse and Deutsch, 2002, using galantamine). There are some positive open label trials of rivastigmine (Lenzi *et al*., 2003;

Mendelsohn *et al*., 2004) in which patients show improvements on standard-rating scales such as Positive and Negative Symptom Scale (PAANS) or BPRS. The study by Lenzi *et al*. (2003) was focused on quality of life measures. The study by Mendelsohn *et al*. (2004) was limited to patients with comorbid dementia, so it may be difficult to generalize the result to the schizophrenic population as a whole.

Some positive findings involving cholinesterase inhibitors were in studies that focused on a specific neurocognitive endophenotype rather than on clinical outcome as a whole. One group found that donepezil normalized fMRI findings on a verbal fluency task (Nahas *et al*., 2003) and another group found that rivastigmine improved performance on a sustained attention task (Aasen *et al*., 2005).

On the negative side, several reports of placebo-controlled, double-blind crossover trials of donepezil show no efficacy against symptoms of schizophrenia. These studies were all done using donepezil as a neuroleptic augmentation treatment. Some (Mazeh *et al*., 2006; Stryjer *et al*., 2003) were in elderly patients or patients with known comorbid dementia. Others were in a general population of stable schizophrenic patients (Friedman *et al*., 2002; Stryjer *et al*., 2004; Tugal *et al*., 2004). No effects were seen on positive, negative, or cognitive symptoms. All of the studies were fairly small, and in some cases there is concern about potential confounding effects of concurrent nicotine use by patients.

Overall, at this time there is little evidence to suggest significant benefits of cholinesterase inhibitors in schizophrenia, especially to patients who do not suffer from comorbid dementia. In some respects, given what we have outlined about the complexity of cholinergic systems, it is not surprising that a class of medications which brings about global increases in ACh levels would have modest effects; in many brain locations, presynaptic inhibition of release may compensate for decreased degradation when ACh levels rise. Thus, given the evidence of effects of treatments targeting nicotinic and muscarinic receptors, it would seem unwarranted to view the modest effects of cholinesterase inhibitors as evidence against participation of cholinergic systems in schizophrenia pathophysiology.

VII. Conclusions

Proper function of cholinergic systems in the brain is essential for a variety of neurocognitive tasks that are impaired in schizophrenia including attention, volition, working memory, assignment of salience, and the processing of sensory information.

While it is unlikely that cholinergic deficits alone account for any particular symptom domain in schizophrenia, there is ample evidence that schizophrenia is associated with genetic changes and brain abnormalities that can influence both the development and function of cholinergic systems, and that interaction of cholinergic deficits with deficits in other systems has the potential to produce disease symptoms.

Perhaps the clearest case of a cholinergic deficit is that of abnormality in the control of α7 nicotinic receptor expression conferring deficits in sensory gating and vulnerability to schizophrenia (cf chapter by Martin and Freedman, this volume). However, it is likely that nicotine has other important sites of action relating to schizophrenia, and that muscarinic effects on corticostriatal and other circuits are of independent import.

Inferences made from clinical and preclinical psychopharmacological data about the performance of cholinergic systems in schizophrenia are fraught with difficulty and do not point to a simple dysregulation of cholinergic transmission at a single brain location. Rather, there are numerous points where dysfunction of particular components of cholinergic signaling can contribute to symptoms or where medications can ameliorate (or worsen) symptoms

regardless of an intrinsic cholinergic deficit. In some instances, these points are uncomfortably close to one another and the effects of cholinergic signaling may be arrayed in opposite directions. In other instances, manipulation of cholinergic systems at one site may be undone by effects of the same manipulation at a distant site. The challenge for neurobiologists and pyschopharmacologists is to find ways to refine our interventions in this complex system and to develop compounds or combinations of compounds which can target sites of interest, without substituting one set of impairments for another.

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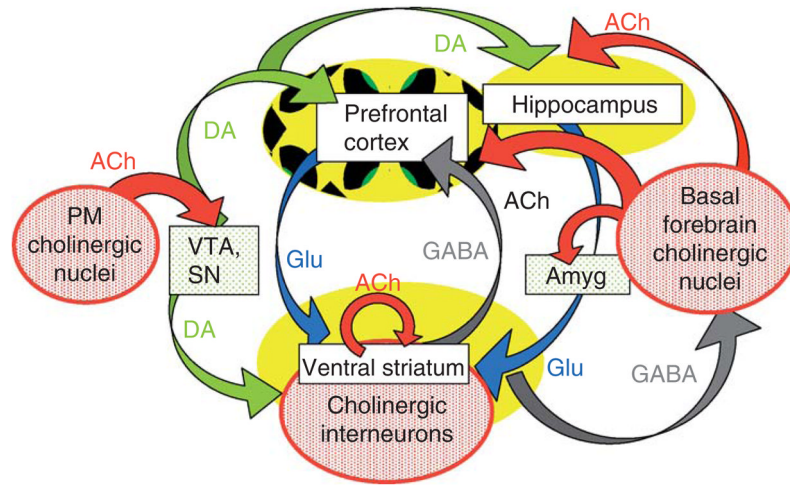
Fig. 1.
Schematic diagram of cholinergic circuits (in red) and their projections within a subset of key brain regions affected in SZ. Cholinergic inputs to prefrontal cortex and hippocampus arise primarily from the basal forebrain group, including the septal cholinergic neurons, the nbM, the preoptic and diagonal band nuclei. Other contributors to the forebrain ACh group are neurons within the substantia innonimata and ventral pallidum. The second major subgroup of ACh-containing neurons, the pontomesencephalic (PM) cholinergic neurons, provides input to brainstem aminergic nuclei (e.g., VTA, SN, and raphe). Cholinergic interneurons intrinsic to the basal ganglia are thought to modulate the relative impact of glutamatergic, dopaminergic, and GABAergic circuits within the ventral striatum. Potential mechanisms of cholinergic regulation of neuronal excitability in prefrontal cortex and hippocampus are also discussed in the text.
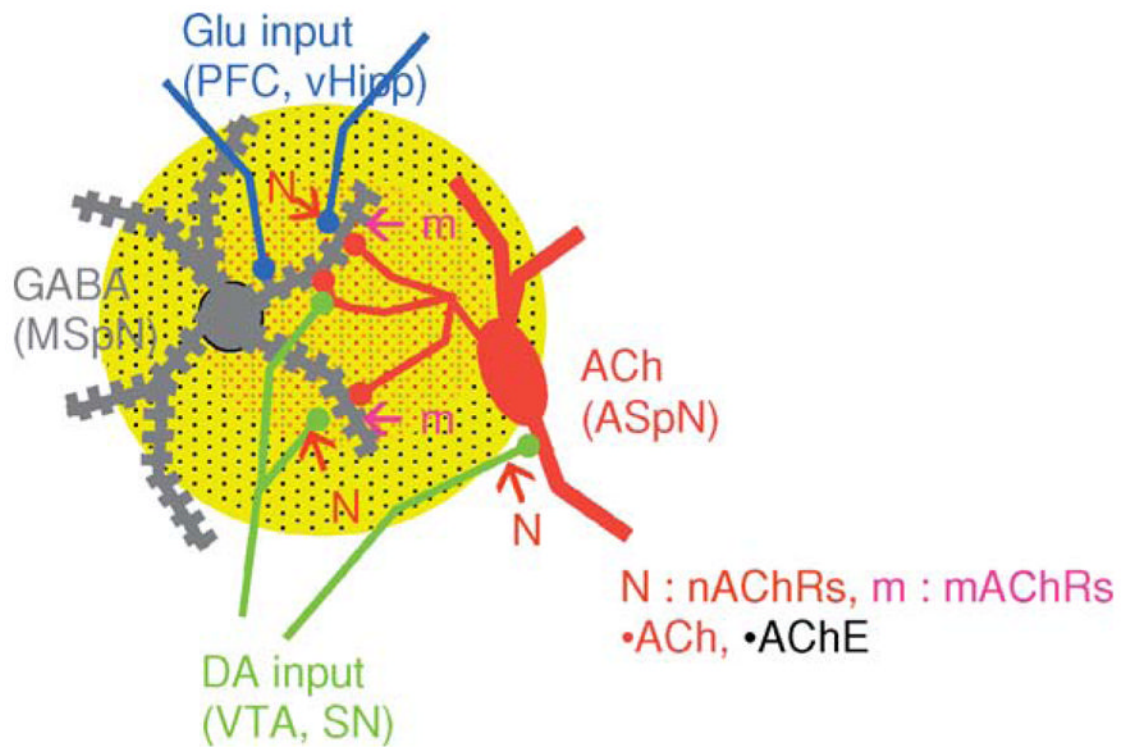
Fig. 2.
Schematic diagram of an aspiny cholinergic neuron (ASpN) and its projections to convergent sites of glutamatergic and dopaminergic input on striatal GABAergic medium spiny projection neurons (MSpN). Changes in local [ACh], from pauses in the firing of these TANS, modulate the net output of the striatum by interactions with ACh receptors and binding sites in pre-, post-, and perisynaptic compartments.