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Review

Modeling cholinergic aspects of schizophrenia: Focus on the antimuscarinic syndrome

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ABSTRACT

Symptoms of schizophrenia, commonly divided into positive symptoms, negative symptoms, and cognitive impairments, exhibit different sensitivity to pharmacological treatments. As such, they are typically modeled in animals by behavioral effects of drugs that evoke these symptoms in humans, such as amphetamine or phencyclidine (PCP). Despite the fact that muscarinic antagonists also evoke a schizophrenia-like syndrome ("antimuscarinic syndrome") and findings of cholinergic-related alterations in brains of schizophrenia patients, modeling schizophrenia using muscarinic manipulations has been infrequently considered, and the effects of muscarinic blockade on behavioral tasks relevant to schizophrenia have not been adequately characterized. The present review surveys recent attempts to model schizophrenia-related symptoms using manipulations causing cholinergic dysfunction, particularly muscarinic blockade, in well validated behavioral models of schizophrenia, such as prepulse inhibition and latent inhibition.

Contents

1. Introduction

Symptoms of schizophrenia are divided into positive symptoms, negative symptoms, and cognitive impairments, a classification which has replaced the notion that cognitive impairments are associated uniquely with negative symptoms [22,32,211]. Treatment of schizophrenia was revolutionized many years ago by the discovery

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that dopaminergic blockers ameliorate the positive symptoms of the disorder. Yet, for decades now, the challenge facing the pharmacotherapy of schizophrenia has been the development of drugs that target negative and, more critically, cognitive symptoms [101,120].

Dysfunctions of the central cholinergic system or degeneration of cholinergic cells are involved in the cognitive symptoms that characterize a wide range of neurological disorders (e.g., Alzheimer's disease, Parkinson's disease [4,5,30,304]). These cognitive deficits, including impairments in memory, thinking and language usage, are also observed in schizophrenia patients [127,239,276] and therefore also may be associated with cholinergic dysfunction in schizophrenia [94,267,303]. Indeed, several lines of evidence suggest an involvement of a cholinergic dysfunction in the pathology of cognitive impairments in schizophrenia, as well as in positive symptoms (for reviews, see refs. [43,68,92,133,208,219,240,315]). Cholinergic involvement in schizophrenia is further supported by the fact that muscarinic antagonists can evoke a psychotic state ("antimuscarinic psychosis/syndrome"), which includes a range of cognitive and psychotic symptoms resembling schizophrenia (see ref. [315], also see below). However, in contrast to the psychosis-inducing drugs from dopamine agonists (DA) (e.g., amphetamine) and *N*-methyl-D-aspartate (NMDA) antagonists (e.g., PCP), whose behavioral effects in animals have been widely used to model schizophrenia [137,247,259], a similar use of muscarinic antagonists has been limited. Given the increasing acknowledgment of cholinergic dysfunction in schizophrenia and the potential benefits of pro-cholinergic drugs for treatment of persistent cognitive impairments in this disorder, this review surveys the use of manipulations causing cholinergic dysfunction in animals, particularly muscarinic blockade, to model schizophrenia.

2. Acetylcholine in the central nervous system – a brief overview

Acetylcholine (ACh) was the first neurotransmitter to be discovered, primarily due to its peripheral function in the somatic and autonomic nervous systems. However, the delineation and characterization of the central cholinergic system are still ongoing, particularly in primate and human brain.

2.1. Cholinergic cell groups and projection pathways

The cholinergic projection neurons are located in two main regions in the brain [183,184,186]. The anterior region, situated in the *basal forebrain* (BF), consists of nuclei in the medial septum and the diagonal band, which project to the hippocampus and the olfactory bulb, respectively, and of the nucleus basalis magnocellularis (NbM; named the nucleus basalis of Meynert in primates and humans), which projects to most of the cortex and to the amygdala [172,182,183]. Together, BF cholinergic nuclei are thought to play a major role in attention, memory, learning and cognition [78,82,209,238,239], and their degeneration (particularly of the NbM) in Alzheimer's disease and other dementias is thought to play a major role in the profound cognitive dysfunction found in these diseases [83,197,304]. The posterior region containing cholinergic cell groups lies in the rostal midbrain (the *mesopontine* area), specifically in the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT) of the pons, and supply cholinergic innervation to the thalamus [183,186], as well as to the ventral tegmental area (VTA), substantia nigra (SN), reticular formation and BF nuclei, among others [28,112,309]. Mesopontine cholinergic cells are implicated in sleep, arousal, cognition and regulation of DA, serotonin and norepinephrine neurotransmission [315]. Two smaller groups of cholinergic cells in the medial habenula and the parabigeminal nucleus projecting to the interpeduncular area and superior colliculus, respectively [185], however, the precise function of these cells is largely unknown. Finally, striatal cholinergic interneurons play a role in motivational processing of the basal ganglia and in the regulation of body weight and metabolism [23,74,121].

2.2. Cholinergic receptors in the CNS

The receptors to which ACh binds are conventionally divided into two types: the metabotropic family of muscarinic receptors and the ionotropic family of nicotinic receptors, named after their prototypical agonists, muscarine and nicotine, respectively (for review, see ref. [172]). Both types of receptors are widely distributed in both the CNS and the PNS. ACh is removed from the synapse primarily by acetylcholinesterase (AChE), which degrades ACh. Thus, AChE inhibitors, which are used in the treatment of dementias, serve to prolong synaptic ACh action.

Nicotinic ACh receptors (nAChRs) are ligand gated ion channels that modulate cell membrane potentials. nAChRs are heterogeneous, with at least six alpha (alpha2–alpha7) and three beta (beta2–beta4) nAChR subunits expressed in mammals. Their homomeric or heteromeric assembly generates multiple nAChR subtypes that differ in their pharmacological and biophysical properties, such as sensitivity to nicotine and rate of desensitization [157]. Two of these subtypes are particularly relevant for cognition: the heteromeric alpha4beta2 and the homomeric alpha7 [92,159,167,212]. Alpha4beta2 nAChR are localized in the interpeduncular nucleus, medial habenula and thalamus. To a lower extent, this receptor subtype is localized in many other areas of the brain, including the cortex, striatum, hippocampus and midbrain nuclei [199]. The alpha7 nAChR are highly available in the cortex and hippocampus [205]. For a comprehensive review on nicotinic receptor structure, function and distribution, see Gotti et al. [111].

Muscarinic acetylcholine receptors (mAChR) belong to the large super-family of plasma membrane-bound G protein coupled receptors, which activate or inhibit second messenger transduction systems. Five highly related muscarinic receptors have been identified (M1–M5). The odd-numbered M1, M3, and M5 receptors activate phospholipase C, therefore they facilitate the inositol phosphate second-messengers that mediates gene expression and other intracellular processes and trigger activation of the phosphoinositide (PI)-coupled receptors. This process is excitatory in action and promotes further neurotransmitter release. In contrast, the M2 and M4 receptors inhibit adenylyl cyclase and modulate calcium and potassium channel function, and are predominately inhibitory in action.

Muscarinic receptor subtypes appear to mediate a variety of pre- and post-synaptic events throughout the CNS. For example, the primarily postsynaptic M1 receptors, which show high density in the cortex, hippocampus and striatum, are thought to play a major role in cognitive function [78]. M2 and M4 receptors, however, are generally thought to mediate pre- or post-synaptic activity. These receptor subtypes have been identified as inhibitory autoreceptors in several brain regions, including the hippocampus, striatum and midbrain, and therefore their selective blockade can be used as a strategy for increasing ACh levels to enhance cognitive function [25,70,78,284,286]. In general, the M1, M3 and M4 mAChRs are abundantly distributed in the brain [42], whereas the M5 subtype appears to be expressed at low levels in the central nervous system [288].

3. Involvement of cholinergic dysfunction in the pathophysiology of schizophrenia

As noted in Section 1, recent years have witnessed a growing focus on cognitive impairments in schizophrenia, leading to

increased efforts to identify treatments that target such impairments. Several lines of evidence have converged to promote the interest in the involvement of the cholinergic system in the pathology of cognitive impairments in schizophrenia and in their treatment (see refs. [43,68,92,133,208,219,240,315]).

3.1. Central cholinergic transmission plays a major role in cognition

The well established correlation between cholinergic dysfunction and/or degeneration and the severity of cognitive impairments in a variety of neurological disorders [4–6,30,104,149,229,304,311] has led to the emergence of the "*cholinergic hypothesis*" of Alzheimer's disease and aging-related cognitive impairments [18,19,280], which essentially states that a loss of cholinergic function in the brain (particularly in the BF) considerably contributes to the cognitive decline associated with advanced age and Alzheimer's disease. During over two decades since the introduction of this hypothesis, substantial efforts have been directed to the understanding of the role of the cholinergic system in cognitive function. Consequently, it has been shown that cholinergic innervation of the cortex and hippocampus plays a fundamental role in attention, learning and memory (for reviews, see refs. [79,83,236]). The cholinergic hypothesis has also led to the development of drug treatments aiming to enhance cognitive function through facilitation of ACh transmission [17,79,86,94,235,267]. Cholinergic cognitive enhancers primarily include AChE inhibitors [24,38,94,225], alpha7 and alpha4beta2 nAChR agonists [53,94,231] and M1 mAChR agonists [43,85,94,103,219,267], but also antagonists of M2 mAChR [155] that increase extracellular ACh levels.

3.2. Cholinergic agonism is a promising strategy for treating cognitive impairments in schizophrenia

Cholinergic stimulation has been suggested as a potential treatment for schizophrenia many years ago [56], but testing the effects of cholinergic agonists in animal models of schizophrenia or in clinical trials have become frequent only in the last two decades. In contrast, cholinergic blockade using antimuscarinic agents has been routinely used to control the extrapyramidal side effects associated with the use of typical antipsychotic drugs (APDs) [68]. In this respect it is important to note that muscarinic antagonists (e.g., scopolamine, atropine) are widely used to induce memory and attentional deficits in animals [27,77], and humans [77,118], and therefore the use of antimuscarinic drugs in schizophrenia patients is likely to exacerbate cognitive impairments in patients.

Enhancement of cholinergic transmission has also been suggested to underlie the beneficial effects of atypical APDs on cognition, compared to typical APDs. Thus, although the capacity of APDs to alleviate cognitive impairments in schizophrenia is limited, atypical APDs may have a relative advantage over typical APDs in this capacity, and the latter has been commonly attributed to the differential effects of these APD classes on regulation of cortical neurotransmission. Deficient cortical DA and ACh transmission is believed to be associated with negative and cognitive symptoms in schizophrenia (e.g., [94,105,106,237]), and it has been shown that atypical, but not typical APDs, increase DA and ACh levels in the cortex [134,135,162,204,287]. Similarly, muscarinic and nicotinic agonists have also been shown to increase ACh and DA levels in the prefrontal cortex (PFC) [26,134,209,212,266], pointing to their potential efficacy in treating negative/cognitive symptoms (for reviews, see refs. [202,219]). This potential has been supported by both animal models and clinical studies, which have shown promising results with nAChR agonists, particularly of the alpha7 and alpha4beta2 receptor subtype [11,52,53,94,152,202,212,245,307], and mAChR agonists, particularly of the M1 and M4 receptor subtype [43,46,67,80,163,164,219,224,252,295]. Furthermore, it has recently been suggested that the main metabolite of clozapine, *N*-desmethylclozapine, increases cortical ACh and DA release in the medial PFC via stimulation of M1 muscarinic receptors and that this may at least partly account for its capacity to treat cognitive symptoms in schizophrenia [67,164,295].

The fact that M1 and M4 mAChRs are both considered as targets for the treatment of schizophrenia symptoms may be puzzling, since as noted above, these receptor subtypes have opposite physiological functions – excitatory *vs.* inhibitory, respectively. These receptor subtypes are also differentially distributed in the brain, and therefore their activation causes different outcomes in different brain areas. Thus, M1 mAChR is most abundant in the cortex and the hippocampus, and its activation has been implicated in cholinergic modulation of attention [86,248], whereas M4 mAChRs are abundant in brain regions rich in dopamine and dopamine receptors such as the midbrain and the striatum, and M4 activation in these locations negatively modulates DA release in the NAC [156,284]. Therefore, it is believed that M1 mAChR agonism is beneficial for cognitive impairments, and this has been shown in animal models and in clinical trials with schizophrenia and dementia patients (for reviews, see refs. [86,156,240,248]). On the contrary, M4 mAChR agonism is considered to be beneficial for positive symptoms, apparently through action on midbrain mAChRs [46,156,284].

In addition to nicotinic and muscarinic specific agonists, non-selective cholinergic treatment using AChE inhibitors has been used for many years for the treatment of cognitive impairments in a range of neurological diseases, particularly Alzheimer's disease [24,38,149]. These drugs inhibit the hydrolysis of ACh, and thus increase ACh levels in the synaptic cleft. The latter can activate both nAChR and mAChR, pre- and post-synapticaly, and therefore can lead to many different site- and dose-dependent consequences. The growing acknowledgment of cholinergic involvement in schizophrenia and the resistance of cognitive impairments in this disorder to APDs [191], have led to many clinical trials using AChE inhibitors, usually as adjunctive treatments. The latter direction has been fortified by the fact that many AChE inhibitors are already available for clinical use.

Three AChE inhibitors have been evaluated for treatment in schizophrenia patients, as well as in animal models of schizophrenia: physostigmine, which is considered the prototypical AChE inhibitor [151], and donezepil and galantamine, which are the most frequently used AChE inhibitors in the clinics [92,269]. Notably, physostigmine and galantamine have also been shown to act as allosteric agonists at nAChRs [207,214,233,234], although they act as inhibitors of nAChRs at higher doses [234]. Preclinical trials using animal models of schizophrenia have shown promising results with all or some of these AChE inhibitors (e.g., [11,12,66,129,289]). However, clinical trials with schizophrenia patients have yielded inconsistent findings (for reviews, see refs. [51,94,268]) and generally pointed to limited effects or no effects of these drugs. Nonetheless, several studies reported that galantamine improved negative and cognitive symptoms of schizophrenia [2,29,230], while donepezil did not [95]. Table 1 summarizes the different cholinergic stimulation strategies suggested as targets for schizophrenia treatment and the symptom domains they aim to treat.

3.3. Postmortem studies show reduction in muscarinic and nicotinic receptors in brains of schizophrenia patients

Studies using radioligands that bind to specific receptors have shown a decreased M1/M4 antagonist radioligand [3H]pirenzepine binding in the caudate-putamen [69], hippocampus [64] and a number of cortical regions [65,71,72,319,320] of schizophrenia patients, pointing to a decreased M1 and/or M4 mAChR density (for

Table 1
Major cholinergic targets suggested for treatment for schizophrenia and the symptom domain they aim to treat.

Drug action	Domain of treatment	Selected references
Muscarinic		
M1 agonist	Cognitive	[43,67,80,163,164,219,248,252,295]
M4 agonist	Positive	[43,46,80,219,224,248,252]
Nicotinic		
α7 Agonist	Cognitive, positive	[11,52,53,94,152,202,212,245,307]
α4β2 Agonist	Cognitive	[53,218,245,305]
Non-specific		
AChE-I	Cognitive	[2,11,12,29,51,66,94,129,230,268,289]

review, see ref. [240]). However, since pirenzepine binds to both M1 and M4 mAChRs, these studies cannot differentiate between these two receptor subtypes, which are very different in their physiological action (see above). Dean et al. [71] have found that M1, but not M4 mAChR protein and mRNA levels are decreased in the brains of schizophrenia patients (also see ref. [174]), suggesting that reduction in primarily cortical M1 mAChRs, rather than M4 mAChRs, is involved in the pathology of schizophrenia. In addition, while no difference has been found in M2/M4 receptor binding in the anterior cingulate cortex [320], it has been found reduced in the striatum [63]. The latter may stem from the reduction of striatal cholinergic interneurons found in schizophrenia patients [131,132]. Importantly, studies in untreated schizophrenia patients and animal studies have ruled out the option that APD treatment is responsible for the modifications in mAChRs [65,292]. It remains to be determined whether down-regulation of these receptors reflects a primary pathological change, or a secondary down-regulation resulting from other alterations in the brains of schizophrenia patients (see ref. [133]).

Postmortem binding studies have also revealed a disturbance of nAChR expression, mostly the alpha7 and alpha4beta2 subunits, in various brain regions (for review, see ref. [227]). Thus, alpha7 binding or protein levels have been found to be reduced in the thalamic reticular nuclei [58,158], hippocampus [34] and frontal cortex [119], and alpha4beta2 binding has been found to be reduced in the striatum [76], hippocampus [93] and cortex [35] of schizophrenia patients. However, these finding might be confounded by heavy smoking in schizophrenia patients, as smoking changes nAChRs expression [227].

Studies examining the integrity of cholinergic cell-groups in brains of schizophrenia patients have usually found no changes in the BF cholinergic cell groups. Conversely, a twofold increase in the number of cholinergic cells in the mesopontine cell groups has been found in elderly schizophrenic patients [99, 148 but see 100], and the activity of mesopontine cell groups has been reported to be reduced [147]. Taken together, these findings suggest the existence of functional and structural abnormalities in the brainstem mesopontine cholinergic cell groups in schizophrenia. Furthermore, since these mesopontine cholinergic cells project to the SN and VTA, these abnormalities may cause schizophrenia-related alterations in DA neurotransmission. In addition, Holt et al. [132,136] have found a decreased density of cholinergic interneurons in the striatum (particularly ventral striatum) of schizophrenia patients, which may also lead to changes in striatal DA transmission.

3.4. Neuroimaging studies show reduction in muscarinic receptors in brains of schizophrenia patients

Consistent with the postmortem studies described above, a recent neuroimaging study has found a decrease in I^{123} quinuclidynil benzilate (QNB) binding in the cortex, the basal ganglia and the thalamus of schizophrenia patients, which points to a reduction in muscarinic receptors in these regions [220]. Moreover, positive symptoms negatively correlated with the availability of muscarinic receptors in the striatum and frontal cortex [220].

3.5. Antimuscarinic psychosis/syndrome mimics positive and cognitive symptoms of schizophrenia

Many muscarinic antagonists (e.g., scopolamine, atropine) can evoke a psychotic state that includes visual, auditory, tactile and olfactory hallucinations, delusions, hyperactivity, stereotypy, severe disruption of attention and thinking, memory loss and confusion (e.g., [54,87,130,175,180,188,208,210,306,315]). At low doses attention is impaired, and individuals experience hallucinations and delusions, while at higher doses individuals become confused and incoherent [87,315]. Noteworthy, in comparison to amphetamine, that induces psychosis characterized by hallucinations and delusions [259], antimuscarinic-induced psychosis includes in addition disorganized thinking, attentional impairments and delirium, characteristic of endogenous schizophrenia [315]. The hallucinations that appear in antimuscarinic psychosis are predominantly visual, while those that appear in endogenous schizophrenia are primarily auditory. However, whereas auditory hallucinations are associated with the early onset of schizophrenia, global severity is associated only with visual hallucinations [196], which are probably more dominant than previously thought, particularly in the chronic phase of the illness [33,196]. Antimuscarinic psychosis can be alleviated by APDs [109,210] as well as by AChE inhibitors [39,109,113,200,210]. In addition, muscarinic antagonists commonly used to reduce extrapyramidal side-effects associated with APD treatment [278], have been reported to exacerbate schizophrenia symptoms and to interfere with the therapeutic effects of APDs [140,168,254,255,279].

The neuropsychopharmacological mechanism of the antimuscarinic syndrome has been suggested to involve blockade of muscarinic inhibitory autoreceptors in the midbrain, causing disruption of the negative feedback loop of ACh transmission. Thus blockade of M2 [315] or M4 [284] inhibitory autoreceptors in the mesopontine cholinergic nuclei has been proposed to cause disinhibition of these nuclei. Since mesopontine cholinergic nuclei supply cholinergic afferents to the SN and VTA, [89,316], this effect is expected to cause an increase in striatal DA levels, leading to hyperactivity, stereotypy and psychosis [82,84,144]. Moreover, this blockade also causes elevated muscarinic activation of the thalamus by mesopontine nuclei, leading to diffused cortical activation and EEG desynchronization that results in poor sensory filtering [315]. In summary, M4 mAChR blockade is thought to play a role in the induction of psychotic symptoms seen in antimuscarinic syndrome, whereas memory and attentional deficits are thought to result from antimuscarinic-induced disruption of hippocampal and cortical cholinergic transmission [315] probably via M1 mAChR [156,240,248]. Thus, the syndrome induced by non-selective muscarinic antagonists may mimic disturbance of cholinergic neurotransmission caused by alteration in the activity and structure of mesopontine nuclei as found in schizophrenia (see above) as well as by alteration in muscarinic receptor availability throughout the brain of schizophrenia patients.

4. Modeling schizophrenia using muscarinic blockade: a potential model of positive and cognitive symptoms in schizophrenia

In spite of the evidence described above for cholinergic involvement in the pathophysiology of schizophrenia, relatively little efforts have been directed to develop and validate cholinergic-based animal models of this disorder. Several reasons converged

to sweep aside "cholinergic modeling" of schizophrenia. Thus, while it is well established that nicotine acts to increase DA release in the nucleus accumbens (NAC) similarly to pro-psychotic drugs such as amphetamine (for reviews, see refs. [9,308]), nicotine does not induce psychosis in humans. In fact, nicotine has long been known to possess pro-cognitive activity in healthy and schizophrenic individuals [123,159], and heavy cigarette smoking among schizophrenia patients has been suggested to serve as self-medication for alleviating symptoms [1]. Likewise, nicotine has been shown to have antipsychotic and pro-cognitive effects in animal models, and to reverse cognitive deficits induced by APDs [159,160,269]. Thus, nicotinic stimulation is considered a treatment strategy (as mentioned above), rather than an approach to model psychosis. In addition, to the best of our knowledge, there has not been any attempt to establish a nicotinic antagonist-based animal model of schizophrenia.

The effects of muscarinic blockade on behavioral tasks relevant to schizophrenia have also not been adequately characterized. The well known scopolamine-induced cognitive deficits [4,27,36,77,264] have been widely used to model cognitive deficits of dementias like Alzheimer's disease (e.g., [165,217]) but have only rarely been considered in terms of relevance to cognitive impairments in schizophrenia, since the latter has been typically pharmacologically modeled using NMDA antagonists [137,153,192]. Thus, although scopolamine has been shown to impair performance in several tasks considered relevant to cognitive impairments seen in schizophrenia, including the five-choice serial reaction time task [206,250], social interaction [261], social recognition [187], reversal learning and attentional set-shifting [48], only few studies assessed the efficacy of APDs to reverse scopolamine-induced cognitive impairments (see refs. [73,187,283]). Consequently, most scopolamine-induced cognitive impairments lack predictive validity for schizophrenia, namely, the capacity to predict the (in)effectiveness of drug treatments relevant for this disorder, which is one of the most important aspects of animal modeling of human diseases. To date, assessments of schizophrenia-related behavioral effects of scopolamine in animals have used almost exclusively models of positive symptoms, particularly locomotor hyperactivity, and disruption of prepulse inhibition (PPI), and latent inhibition (LI). APDs and cognition enhancing drugs have been tested on these models, providing predictive validity to some of these models. Table 2 summarizes the effects of muscarinic manipulations on locomotor activity, PPI and LI, and their response to drug treatments.

4.1. Locomotor activity and stereotypy

Stimulation of the dopaminergic system with DA agonists amphetamine or apomorphine leads to an increased locomotor activity, which progresses to stereotypy at high doses [259], and these effects are blocked by APDs (e.g., [7]). The locomotor effects of DA agonists have long been considered to model positive symptoms of schizophrenia (e.g., [260]). Systemic administration of scopolamine also results in locomotor hyperactivity and stereotypy [50,251,256]. These behavioral effects of scopolamine are reversed by cholinomimetic drugs such as the AChE inhibitor physostigmine as well as by APDs [177,251]. Consequently, hyperactivity induced by muscarinic blockade has been suggested to model antimuscarinic psychosis, and perhaps cholinergic-related psychosis in schizophrenia (see refs. [177,315]).

Because administration of muscarinic antagonists increases DA influx in the striatum [47], muscarinic antagonist-induced hyperactivity has been typically attributed to this action [177,314]. More specifically, it has been proposed that muscarinic antagonists increase ACh transmission near midbrain dopaminergic nuclei (VTA and SN) by blocking M2/M4 inhibitory autoreceptors in the mesopontine cholinergic nuclei [284,315]. This leads to overactivation of midbrain dopaminergic nuclei and to elevation in striatal/accumbal DA levels. Indeed, the dopaminergic D1 and D1/D2 antagonists SCH 23390 and haloperidol, respectively, reversed scopolamine-induced hyperactivity [251], and infusion of scopolamine into the PPT in the midbrain increased DA efflux in the striatum as well as stereotypy, locomotor activity, and brain stimulation reward, similarly to effects of systemically injected amphetamine [47,313,315,316]. Furthermore, infusion of the cholinergic agonist carbachol into the PPT reduced both stereotypy and locomotion produced by systemic scopolamine [177], indicating that scopolamine-induced hyperactivity is related to its action at muscarinic receptors in this brain region. DA–ACh interaction can cause hyperactivity also at the striatal level. Thus, the dopaminergic agonists quinpirole, apomorphine and S-(−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine reversed scopolamine-induced hyperactivity, an effect that was suggested to stem from cholinergic–dopaminergic interplay resulting in increased striatal ACh levels that competed with scopolamine at muscarinic receptors [251]. Interestingly, BF cholinergic nuclei projecting to the cortex may also play a role in the modulation of locomotor activity, because selective depletion of these projections enhance amphetamine-induced locomotor activity, while selective depletion of cholinergic projections to the hippocampus has no such effect [178].

The insufficiency of pharmacological ligands that are selective for muscarinic receptor subtypes has led investigators to use mAChR knockout mice to investigate which receptor subtypes may regulate locomotor behaviors. In consistence with the scheme discussed above, M4 mAChR knockout mice exhibit higher spontaneous locomotor activity and are more responsive to apomorphine and SKF 38393 (a partial D1 agonist) than their wild type controls [108]. In contrast, M2 mAChR knockout mice show no locomotor hyperactivity [107], suggesting that M4 mAChRs are more important than M2 mAChR in the regulation of locomotor activity, in line with the findings of their differential role in the activation of midbrain ACh and DA nuclei [284]. Relatedly, scopolamine-induced hyperactivity was resistant to the muscarinic agonists oxotremorine, RS86 and pilocarpine, which are considered to act predominantly on M2 and M3 mAChRs [251], strengthening the suggestion that these receptor subtypes play minimal role in antimuscarinic-induced locomotor hyperactivity.

Recently, it has been shown that M5 mutant mice exhibit decreased amphetamine-induced locomotor activity [290], but increased scopolamine-induced or M1 antagonist trihexyphenidyl-induced locomotor activity [49,283]. While the former finding is consistent with reports that m5 gene deletion reduces striatal/accumbal DA release [90,322], the latter findings suggest that M5 receptor activation normally inhibits scopolamine-induced hyper-locomotion. Moreover, while the findings discussed above suggest that muscarinic blockade causes hyperactivity through modulation of striatal DA levels, similarly to amphetamine, the findings with M5 mutant mice imply that the capacity of scopolamine or trihexyphenidyl to increase locomotor activity can be independent from their capacity to increase striatal DA levels. In support to the latter, M1 antagonists telenzepine and trihexyphenidyl increased locomotor activity levels without affecting striatal/accumbal DA levels [277], suggesting that the effects of scopolamine on locomotor activity might be mediated also by non-dopaminergic mechanisms, such as modulation of glutamate transmission (see ref. [270]).

Taken as a whole, these findings suggest that muscarinic blockade can induce locomotor hyperactivity via at least two separate mechanisms: elevation of striatal/accumbal DA levels through disruption of cholinergic negative feedback loops in the midbrain; and non-dopaminergic mechanisms, which are likely to involve modulation of excitatory neurotransmission. The latter mechanism

Table 2
Effects of muscarinic manipulations on locomotor activity, prepulse inhibition and latent inhibition, and their response to drug treatments. ↓ and ↑ indicate decrease and increase, respectively, in the phenomenon (*abbreviations*: AChE, acetylcholinesterase; BLA, basolateral amygdala; EC, entorhinal cortex; IC, insular cortex; i.c.v., intracerebroventricular injection; PPT, pedunculopontine tegmental nucleus; VTA, ventral tegmental area).

Muscarinic manipulation	Effect of manipulation	Treatment used	Effect of treatment	References
Locomotor activity				
Muscarinic antagonists: scopolamine, atropine, azaprophen, biperiden, scopolamine, trihexyphenidyl	↑	*AChE inhibitors*: physostigmine, tetrahydroaminoacridine hydrate	↓	[50,251,256]
		Muscarinic agonists: oxotremorine, RS86, pilocarpine	No effect	
		Dopamine agonists: quinpirole, apomorphine, S-(−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine	↓	
		Amphetamine	↑	
		SCH 23390 (D1 antagonist), haloperidol (D2 antagonist)	↓	
		Intra-VTA dihydro-β-erythroidine (DHBE; nicotinic antagonist)	No effect	
Intra-PPT scopolamine	↑	Intra-PPT carbachol (muscarinic agonist)	↓	[177]
		Haloperidol (systemic)	↓	
Intra-caudal pontine reticular nucleus scopolamine	↑	–		[81]
M2 knockout mice	No effect	–		[107]
Telenzepine (M1 antagonist) Trihexyphenidyl (M1 muscarinic antagonist)	↑	Cocaine	↓ ↑	[277]
M5 knockout mice	No effect	Amphetamine	↓	[50,281,290]
		Scopolamine	↑	
		Trihexyphenidyl (M1 antagonist)	↑	
Prepulse inhibition				
Muscarinic antagonists: scopolamine, trihexyphenidyl, benztropine, benactyzine, biperiden, 4-DAMP (i.c.v.), tropicamide (i.c.v.)	↓	Oxotremorine	↑	[3,129,141–143,190,256,266,285,310]
		AChE inhibitors: galantamine, donepezil	↑	
		Haloperidol, xanomeline (M1/4 agonist)	↑	
		SCH23390 (D1 antagonist)	No effect	
		RO-4368854 (5-HT6 antagonist)	No effect	
Muscarinic antagonists: dicyclomine, biperiden, pirenzepine (i.c.v.), AF-DX116 (i.c.v.)	No effect	–		[143,285]
Muscarinic agonists: pilocarpine, oxotremorine, RS-86, arecoline	No effect	–		
Procyclidine (M1/M2/M4 antagonist)	↓ In humans	–		
M5 knockout mice	↓	Clozapine	↑	[281]
		Haloperidol	No reversal	
Intra-caudal pontine reticular nucleus scopolamine	↓	–		[81]
Intra-caudal pontine reticular nucleus carbachol	↑	–		
Latent inhibition				
Scopolamine	↓	Haloperidol, clozapine, physostigmine, glycine, xanomeline	↑	[13,44]; Barak and Weiner, unpublished observations
Scopolamine	No effect	–		[193]
Scopolamine	↑	Physostigmine, glycine, xanomeline	↓	[15]; Barak and Weiner, unpublished observations
M5 mutant mice	↑	–		[289]
Intra-EC or intra-IC scopolamine	↓	–		[14,189,198]
Intra-BLA scopolamine	↑	–		Barak and Weiner, unpublished observations

dissociates between scopolamine- and amphetamine-induced hyperactivity, and by corollary dissociates between the psychoses these compounds may model. Thus, muscarinic blockade-induced locomotor hyperactivity may model cholinergic-related positive symptoms that may differ from the dopaminergic-related psychosis conventionally modeled by amphetamine-induced hyperactivity.

4.2. Prepulse inhibition

Another widely used animal model of schizophrenia in which muscarinic agents have been shown to be active is the prepulse inhibition model. PPI refers to the observation that the presentation of a brief, non-startling tactile, acoustic or visual stimulus immediately prior to a more intense stimulus, reduces the startle response to the latter stimulus. This phenomenon, which is considered to index the ability to "gate out" sensorimotor input, is disrupted in schizophrenia patients and can be restored by APD treatment [275,293], and therefore its disruption in rodents is considered to model sensorimotor gating deficits in schizophrenia [102,271]. In the rat, PPI is disrupted following the administration of the DA agonists amphetamine and apomorphine and by NMDA antagonists such as PCP, MK-801 and ketamine. While the effects of DA agonists are reversed by typical and atypical APDs, the effects of NMDA antagonists in this model are selectively reversed by atypical APDs [102 but see 213], suggesting that the NMDA antagonist PPI model can dissociate between typical and atypical APDs.

Consistent with their psychotomimetic effects on humans, muscarinic antagonists such as scopolamine have been shown to disrupt PPI [3,129,141–143,190,257,266,285,310]. The antimuscarinic agent procyclidine, which antagonizes primarily M1, M2 and M4 mAChRs has disrupted PPI also in healthy humans [154]. In mice, the M1 preferring antagonist pirenzepine and the M2 antagonist AF-DX116 spared PPI, whereas the M3 antagonist 4-DAMP and the M4 antagonist tropicamide attenuated PPI [285], suggesting that cholinergic regulation of PPI occurs via muscarinic M3 and M4 mAChRs. These findings suggest that muscarinic blockade-induced disruption of PPI may result from blockade of M4 inhibitory autoreceptors in the midbrain. The latter would lead to an overactivation of dopaminergic midbrain nuclei and increased striatal/accumbal DA levels, which is known to be associated with disruption of PPI [272]. However, M5 mAChR knockout mice, which have *reduced* striatal/accumbal DA levels [91,321], have also shown decreased PPI [281] suggesting that an additional, non-dopaminergic mechanism, may underlie disrupted PPI induced by muscarinic dysfunction. An alternative mechanism proposed by Fendt et al. [82] postulates that muscarinic and GABA-B inhibitory receptors on the caudal pontine reticular nucleus giant neurons combine to produce the long-lasting inhibition of startle. In addition, PPI has also been shown to be disrupted after bilateral lesion of the NbM in the BF, and restored by the AChE inhibitor rivastigmine [10], suggesting that cholinergic innervation of the cortex plays a role in the expression of PPI. While the specific mechanisms underlying muscarinic antagonist-induced disrupted PPI remain to be elucidated, the above findings suggest that these mechanisms are distinct from those underlying DA agonist-induced disrupted PPI. Consequently, PPI disruption caused by these two drug classes may mimic different pathological mechanisms underlying schizophrenia symptoms.

The pharmacological profile of muscarinic antagonist-induced disruption of PPI, however, does not seem to differ significantly from that of DA agonist-induced disruption of PPI. Thus, scopolamine-induced disruption of PPI can be reversed by cholinomimetics like the muscarinic non-selective agonist oxotremorine [143], M1/M4 agonist xanomeline [141] or the AChE inhibitors galantamine and donepezil [129] as well as by the APD haloperidol [141], similarly to apomorphine-induced disrupted PPI [102,129,141,266]. Despite this similarity, dissociation between the effects of these two drugs on PPI was obtained when apomorphine-, but not scopolamine-induced disruption of PPI was reversed by a 5-HT6 antagonist [190]. In addition, disrupted PPI in M5 mAChR knockout mice could be reversed by clozapine [281] but not haloperidol. This finding suggests that unlike PPI disruption induced by scopolamine or apomorphine, this mouse mutation may have the potential capacity to dissociate between typical and atypical APDs. Furthermore, since atypical APDs are more effective than typical APDs in treating negative/cognitive symptoms [8,40,150], M5 mAChR deletion can model negative/cognitive symptoms associated with cholinergic dysfunction.

In summary, the effects of muscarinic manipulations on PPI support the involvement of these receptors in sensorimotor gating deficits seen in schizophrenia. More specifically, the capacity of muscarinic blockade to disrupt PPI, taken together with the pharmacological characterization of this PPI disruption, suggests that the latter may model antimuscarinic-induced psychotic symptoms, as well as cholinergic-related positive symptoms in schizophrenia. While current schemes suggest that scopolamine disrupts PPI by elevating dopaminergic transmission, or alternatively by cholinergic modulation of other neurotransmission systems, the exact mechanism remains to be determined. A better understanding of the mechanisms underlying disruption of PPI induced by muscarinic manipulations may promote the understanding of the mechanisms underlying positive symptoms caused by muscarinic dysfunction.

4.3. Latent inhibition

Latent inhibition is a cross-species selective attention phenomenon, in which organisms learn to ignore, or to inattend to, stimuli that were experienced as irrelevant in the past [170,173]. LI is manifested as poorer conditioning to a stimulus when the stage of conditioning is preceded by a stage of repeated non-reinforced pre-exposure to that stimulus.

Loss of LI induced by amphetamine is a well established model of positive symptoms of schizophrenia (for reviews, see refs. [114,195,296–298]), fortified by findings of disrupted LI in amphetamine-treated normal humans [116,232,273,282] and in acute schizophrenia patients [20,115, 117, 223, but also see 274]. Consistent with the pharmacology of positive symptoms, amphetamine-induced LI disruption is reversed by both typical and atypical APDs. When given on their own, APDs potentiate LI in rats and humans under conditions that do not suffice to yield LI in no-drug controls (such as weak pre-exposure or strong conditioning; [110,249,291,301]). Conversely, low doses of NMDA antagonists produce strong LI under conditions that yield weak or no LI in no-drug controls [96,97,166,203]. We have suggested that LI persistence may provide a correlate of a specific aspect of negative/cognitive symptomatology, namely, attentional perseveration, or impaired set shifting [96,97]. This has been supported by recent demonstrations of excessively strong LI in schizophrenia patients, which is positively correlated with negative symptoms severity [55,223]. Furthermore, persistent LI following MK-801 treatment is resistant to typical APDs but is reversed by atypical APDs and by compounds enhancing NMDA function via the glycineB site [96,97,166], which are considered to be beneficial in the treatment of negative symptoms in schizophrenia patients [126,181].

Latent inhibition and the central cholinergic system. Although LI is considered a manifestations of attentional selectivity in associative learning [170,173], and ACh has been shown to play a key role in attentional processing [125,236], there has not been a systematic investigation of the effects of cholinergic manipulations on LI. Lesion studies of forebrain cholinergic cells groups (NbM, Ch4) have yielded inconsistent findings: NbM lesion has been reported to disrupt LI [228,302], or to spare it [241]. In addition, selective lesion of septohippocampal cholinergic projections from the fore-

brain medial septum/vertical limb of the diagonal band has been reported to spare LI in a conditioned taste aversion procedure [75], but to disrupt it in an appetitive procedure [21]. No studies have tested the involvement of midbrain cholinergic cell groups in LI.

4.3.1. The antimuscarinic LI model of schizophrenia

Only a few studies using muscarinic manipulations in LI have been published until recently. Both systemic [44] and intra-insular cortex (IC) [189,198] administration of scopolamine to rats before pre-exposure have disrupted LI. However, Moore et al. [193] have found that scopolamine injected in both pre-exposure and conditioning does not affect LI in rabbits. Finally, M5 mutant mice exhibited persistent LI [290]. Taken together, these finding imply that muscarinic manipulations can lead to opposite aberrations of LI, namely disruption or persistence, which are considered to model positive and negative/cognitive symptoms in schizophrenia, respectively. While the latter is consistent with the capacity of antimuscarinic drugs to induce both psychosis and cognitive impairments (see above), clearly further characterization of the effects of scopolamine on LI is required in order to promote the understanding of these findings.

4.3.1.1. Modeling cholinergic-related positive symptoms. Recently, we have begun a systematic investigation of the effects of muscarinic blockade on LI, with the aim of establishing an antimuscarinic LI model of schizophrenia. In a first series of experiments, we [13] showed that scopolamine disrupted LI at low doses (0.15 or 0.5 mg/kg). We found that this effect was due to the action of the drug in the pre-exposure stage of the LI procedure, suggesting that scopolamine disrupted LI by impairing the ability to in-attend to irrelevant stimuli. Both the typical and the atypical APDs, haloperidol and clozapine, reversed scopolamine-induced LI disruption when given in conditioning but not in pre-exposure, indicating that the mechanism of antipsychotic action in this model is independent of the mechanism of action of the pro-psychotic drug. Scopolamine-induced LI disruption was also reversed by the AChE inhibitor physostigmine [13], the M1/M4 mAChR agonist xanomeline, and the NMDA allosteric agonist glycine (Barak and Weiner, unpublished observations). Our findings indicate that the pharmacological profile of scopolamine-induced disrupted LI is distinct from that of amphetamine-induced disrupted LI, whereby the latter is resistant to physostigmine and glycine. Furthermore, our finding that scopolamine acts in the pre-exposure stage to disrupt LI, unlike amphetamine, which disrupts LI via action in the conditioning stage, provides additional evidence for different mechanisms underlying LI disruption induced by these two drugs (see Weiner and Arad, 2009, in this issue). Relatedly, we have suggested that scopolamine-induced LI disruption may model the positive spectrum symptoms of the antimuscarinic psychosis, which is distinct from that of dopaminergic psychosis.

4.3.1.2. Modeling cholinergic-related APD-resistant cognitive impairments. As mentioned above, the antimuscarinic syndrome includes both positive symptoms and cognitive impairments, but only the former aspect has been modeled in animal models of schizophrenia that possess predictive validity. Thus, cognitive impairments induced by scopolamine have been shown to be reversed by cognitive enhancers from both the cholinomimetic (e.g., [4,128,206,212]) and glycine agonist [88,201,258] classes, but the effectiveness of APDs in these studies has not been tested. Since cognitive impairments in schizophrenia show little if any improvement following APD treatment [41,191], an animal model of schizophrenia that accounts for resistance to APDs but is sensitive to cholinergic and glycinergic cognitive enhancers may have considerable utility for screening of cognitive enhancers for treatment of APD-resistant cognitive impairments in this disorder. We have obtained preliminary evidence for such an animal model by using a stronger muscarinic blockade than the one we used to model cholinergic-related positive symptoms [15].

In contrast to low scopolamine doses, we have found that the higher dose of 1 mg/kg scopolamine spares LI [13]. Three reasons have led us to entertain the possibility that high doses would induce persistent LI. First, muscarinic antagonists produce a syndrome that includes in addition to the psychotic-like effects also cognitive impairments, the latter appearing at higher doses [315]. Second, many lesion and drug manipulations which spare LI under conditions that yield LI in control rats, produce LI persistence when tested under conditions that disrupt LI in control rats (for review, see ref. [297]). Third, scopolamine has been shown to produce perseverative behaviors [48,221,262] and persistent LI is a form of a perseverative behavior [97]. Indeed, we showed that at 1.5 mg/kg, scopolamine induced abnormally persistent LI [15]. Unlike disrupted LI induced by scopolamine, this drug induced persistence of LI due to its action in the conditioning stage, suggesting that scopolamine prevents re-attention to previously irrelevant stimuli that became motivationally relevant through pairings with reinforcement. The pharmacological profile of scopolamine-induced *persistent LI* is also different from that of scopolamine-induced *disrupted LI*. Thus, while scopolamine-induced persistent LI is reversed by the cognition enhancing drugs glycine, physostigmine [15] and xanomeline (Barak and Weiner, unpublished observations), it is unaffected by haloperidol and clozapine. Consequently, we [15] suggested that scopolamine-induced persistent LI may provide a novel model that displays sensitivity to cognitive enhancers, but is resistant to APDs.

Obviously, additional studies are required, testing a range of cognitive enhancers and APDs from different classes, to validate the selective sensitivity of scopolamine-induced persistent LI to the former class of drugs, as well as the mechanisms of such pharmacological selectivity. However, given the pharmacological profile described above, which provides preliminary evidence that scopolamine-induced persistent LI is an APD-resistant cognitive impairment, we have suggested that it may model APD-resistant cognitive impairments in schizophrenia [15]. Furthermore, given its sensitivity to cognitive enhancers, scopolamine-induced persistent LI may have a considerable utility in detecting effective treatments for APD-resistant cognitive impairments in schizophrenia. It should be noted, however, that abnormally persistent LI which is insensitive to APDs may represent a more general form of behavioral perseveration, which is common to a variety of neuropsychiatric disorders, including schizophrenia, autism, addictive behavior and obsessive compulsive disorders (e.g., [45,62,157,222,226]).

4.3.1.3. Neuropsychopharmacological differentiation between the opposite effects of scopolamine on LI. The capacity of systemic scopolamine to induce opposite effects on LI, namely disrupted LI at low doses and persistent LI at a higher-moderate dose, has led us to investigate whether these opposing behavioral effects of scopolamine on LI would be dissociable psychologically and neuropharmacologically.

Psychological dissociation. In terms of psychological processes underlying LI, it is believed that during pre-exposure, the acquisition of an association between the pre-exposed stimulus and the absence of a significant consequence reduces the salience, or the significance of the stimulus, which impairs the acquisition of the stimulus-reinforcement association in conditioning [169,173] or on more recent accounts, inhibits the expression of the conditioned response resulting from stimulus–reinforcement association acquired during conditioning [31,114,171,296,297] Strong conditioning overrides the inhibitory influence of the inattentional response so that animals switch to respond according to the more recent stimulus–reinforcement relationship [294,297]. Thus,

scopolamine produces opposite poles of impairment in attentional selectivity: at low doses it impairs the capacity to inattend to irrelevant stimuli, whereas at a higher dose it impairs the capacity to re-attend to previously irrelevant stimuli that regained relevance through by signaling significant outcomes. It should be noted, however, that both disruption and persistence of LI can stem from drug action in pre-exposure (impairment or facilitation, respectively, of learned inattention), or in conditioning (facilitation or impairment, respectively, of switching to respond according to stimulus-reinforcement association). Low doses of scopolamine disrupt LI due to the action of the drug in the pre-exposure stage, and thus presumably reflect impaired acquisition of inattention [13]. Conversely, the higher dose induces persistent LI by hindering the process of updating/adjusting the response to the stimulus-reinforcement contingency in the conditioning stage [15]. Thus, scopolamine induces disruption and persistence of LI by impairing different psychological/attentional process, occurring at different stages of the LI procedure.

Neuropharmacological dissociation. Recently we tested the hypothesis that the dose-dependent contrasting effects of scopo-

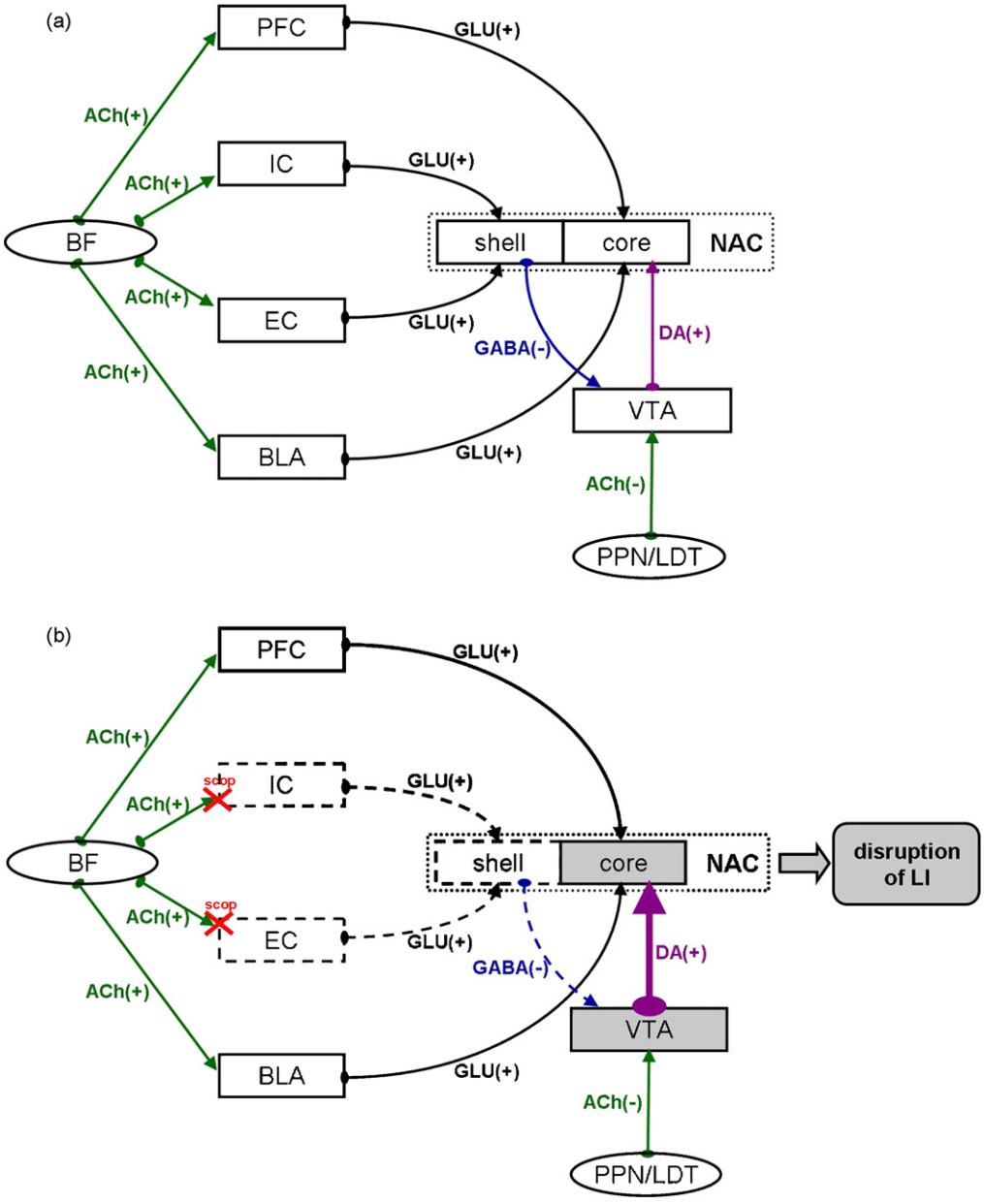

Fig. 1. Neural circuitry through which cholinergic projections modulate the expression of latent inhibition. *Abbreviations*: ACh, acetylcholine; BF, basal forebrain; BLA, basolateral amygdala; DA, dopamine; EC, entorhinal cortex; GLU glutamate; IC, insular cortex; LDT, laterodorsal tegmental nucleus; LI, latent inhibition; NAC, nucleus accumbens; PFC, prefrontal cortex; PPN, pedunculopontine tegmental nucleus; SCOP, scopolamine; VTA, ventral tegmental area. (a) The PFC, EC, IC and BLA receive cholinergic afferents from the BF. Projections from the PFC and the BLA to the NAC core, and from the EC and IC to the NAC shell enhance and reduce, respectively, DA release from the VTA to the NAC core. Increased and decreased DA levels in the NAC core are associated with LI disruption and persistence, respectively. In addition, cholinergic afferents from the midbrain cholinergic nuclei PPN/LDT to the VTA negatively modulated DA release in the NAC. (b) Muscarinic blockade in the EC or IC inhibits the inputs of these regions to the NAC shell, causing disinhibition of the VTA and enhancing DA release in the NAC core, and leading to disruption of LI. (c) Muscarinic blockade in the BLA inhibits the inputs of these brain regions to the NAC core. Concurrently, the NAC shell, which receives excitatory inputs from the IC and EC, sends inhibitory inputs to the VTA, reducing DA release in the NAC core. Both of these effects lead to LI persistence. Intra-PFC scopolamine infusion is expected to affect LI similarly. (d) Muscarinic antagonists in the midbrain (VTA or PPN/LDT) block inhibitory M4 muscarinic mAChRs, leading to enhanced stimulation of the VTA and to enhanced DA influx in the NAC core. Thus, muscarinic blockade in these midbrain nuclei would be expected to disrupt LI. This model is based on the switching model of LI [296–298], models of cholinergic-related circuitries mediating attentional processing [125,238,284,315], and LI studies using muscarinic antagonists.

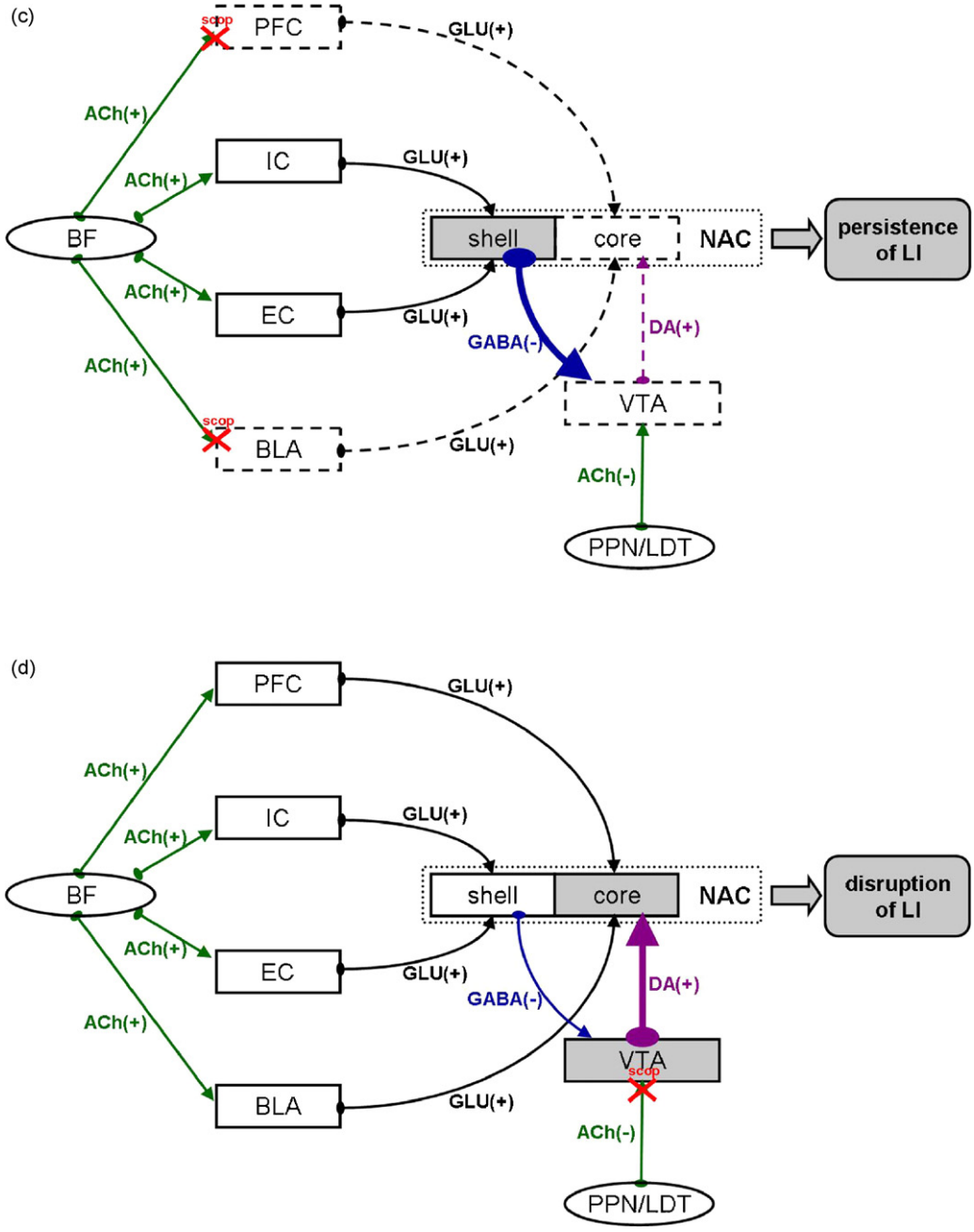

Fig. 1. (*Continued.*)

lamine also reflect an action of the drug at different locations in the brain during the different stages of the procedure. Investigations of the neural substrates of LI in the rat have pointed to a critical involvement of the NAC in this phenomenon. Young et al. [318] have shown that while the presentation of a stimulus previously paired with a shock enhances DA release in the NAC, pre-exposure to that stimulus markedly attenuates this effect. It has also been shown that intra-accumbens infusion of amphetamine disrupts LI [263] whereas intra-accumbens infusion of haloperidol blocks amphetamine-induced disruption of LI, and potentiates LI [145]. There is a clear functional differentiation between the shell and the core subregions of the NAC with shell lesions leading to disruption of LI, and core lesions inducing persistent LI [98,243,299,300].

The neural circuitry of LI includes several brain regions which provide major inputs to the NAC, including the entorhinal cortex (EC), and the basolateral amygdala (BLA). It has been shown that EC lesions [60,61,253,312] as well as its inactivation during the pre-exposure stage [138,161] disrupt LI, and this effect has been attributed to the lesion-induced alterations in DA transmission in the NAC shell and anterior striatum [138]. Recent findings suggest that cholinergic innervations of the EC play a critical role in the encoding of novel, but not of familiar stimuli [124,125,179], raising the possibility that cholinergic transmission in the EC might also play a role in LI. This possibility is strengthened by our finding that scopolamine disrupts LI by acting in the pre-exposure stage [13], similarly to EC inactivation. This has led us to test the effects of muscarinic blockade in the EC on LI, using a local infusion of scopolamine. Indeed, we have found that intra-EC scopolamine disrupts LI when infused in pre-exposure or in both pre-exposure and conditioning, but not if it is confined to conditioning [14]. While cholinergic innervation of the EC has long been postulated to be involved in the attention to, and encoding of, novel stim-

uli, our findings provide first evidence that it also plays a crucial role in the development of inattention to stimuli. Moreover, our findings suggest that mAChRs in the EC mediate acquisition of inattention. Thus, muscarinic dysfunction in the EC may underlie not only working memory deficits and impaired ability to maintain attention to significant stimuli, but also cognitive over-switching/distractibility caused by impaired ability to in-attend to irrelevant stimuli, that are associated with psychotic symptoms in schizophrenia [114,122,146,296,297,317].

In contrast to the effects of EC lesion, BLA lesion have been shown to lead to persistent LI [242, 243, 297 but see 59]. BLA has been suggested to provide information regarding the current motivational/affective value of the conditioned stimulus (e.g., [57,139,244,265]), which in the case of LI, determine whether LI is present or disrupted [242,297]. The fact that cholinergic innervation of the BLA plays an important role in learning and memory consolidation and that this role is mediated by mAChRs [16,215,216,246], has led us to hypothesize that muscarinic blockade in the BLA will replicate the effects of systemic scopolamine at high doses on LI, namely, will induce persistent LI. We have found that infusion of scopolamine into the BLA with conditions that yields LI in controls does not affect LI, but under strong conditioning, which prevents the expression of LI in controls, muscarinic blockade in the BLA induces persistent LI (Barak and Weiner, unpublished observations). Furthermore, persistent LI has been induced when the infusion of scopolamine is confined to the conditioning stage, but not when confined to the pre-exposure stage. The latter parallels our results with systemic high doses of scopolamine, suggesting that persistent LI induced by scopolamine is due to the action of this drug at mAChRs in the BLA. More generally, muscarinic receptors in the BLA may mediate re-allocation of attention to previously irrelevant stimuli when they signal valuable outcomes. This implies that muscarinic dysfunction in the BLA may underlie cognitive inflexibility and attentional perseveration, which are associated with negative/cognitive symptoms in schizophrenia [62,157,194,317].

Fig. 1a presents a scheme of cholinergic modulation of LI expression. The scheme is based on the switching model of LI (Weiner [296,297]), known effects of muscarinic blockade on LI, and models of cholinergic-related circuitries mediating attentional processing [125,238,284,315]. The PFC, EC, IC and BLA receive cholinergic afferents from the BF. Projections from the PFC and the BLA to the NAC core, and from the EC and IC to the NAC shell [37,49,297,298] enhance and reduce, respectively, DA release from the VTA to the NAC core. Increased and decreased DA levels in the NAC core are associated with LI disruption and persistence, respectively [294,297,298]. In addition, cholinergic afferents from the midbrain cholinergic nuclei PPN/LDT to the VTA negatively modulate DA release in the NAC.

Muscarinic blockade in the EC or IC inhibits the inputs of these regions to the NAC shell, causing disinhibition of the VTA and enhancing DA release in the NAC core, and thus leading to LI disruption. The latter is also promoted by concurrent excitatory inputs from the PFC and the BLA to the NAC core (see Fig. 1b). Muscarinic blockade in the BLA inhibits the inputs of this brain region to the NAC core; concurrently, the NAC shell, which receives excitatory inputs from the IC and EC, sends inhibitory inputs to the VTA, reducing DA release in the NAC core. Both of these effects lead to LI persistence (see Fig. 1c). Intra-PFC scopolamine is expected to affect LI similarly. Finally, muscarinic antagonists in the midbrain (VTA or PPN/LDT) block inhibitory M4 muscarinic mAChRs, leading to enhanced stimulation of the VTA and to enhanced DA influx in the NAC core [284,315,316] (see Fig. 1d). Thus, muscarinic blockade in these midbrain nuclei would also be expected to disrupt LI.

This model implies that muscarinic transmission in the regions described in the model mediate normal attentional processing. Relatedly, abnormalities in muscarinic cholinergic transmission in these brain regions may underlie two poles of attentional aberrations: distractibility caused by impaired ability to in-attend to irrelevant stimuli, mediated by muscarinic transmission in the EC, the IC and and/or the midbrain; and cognitive rigidity caused by impaired ability re-attend to stimuli that regain relevance, mediated by muscarinic transmission in the BLA and the PFC.

5. Summary and conclusions

In recent years, the search for drugs that would treat cognitive impairments in schizophrenia has become one of the major challenges in the field [101,120]. In this endeavor, valid animal models of schizophrenia play a crucial role. Indeed, preclinical assessment tools for the cognition enhancing capacity of novel drugs have been developed and established [101; MATRICS project – http://www.matrics.ucla.edu]. Given the well-documented involvement of the cholinergic system in cognition, it has been acknowledged that cholinergic compound may provide a leading target for developing drugs that would show efficacy for cognition enhancement in schizophrenia [41,176].

In light of the accumulating clinical evidence for cholinergic, particularly muscarinic dysfunction in the brains of schizophrenia patients and for a schizophrenia-like syndrome induced by muscarinic antagonists, the effects of muscarinic manipulations have been assessed in several animal models relevant to schizophrenia. However, although the antimuscarinic syndrome usually consists of both psychosis and cognitive impairments, most attempts to model schizophrenia symptoms using muscarinic blockade have concentrated on the positive spectrum of symptoms, and neglected cognitive impairments. Thus, most existing data in animals show that muscarinic blockade induces behavioral alterations considered to model, and to be predictive of activity against, positive symptoms of schizophrenia, implying that the cholinergic muscarinic system plays a role in attentional/cognitive processes underlying psychosis. Although the behavioral manifestations induced by muscarinic blockade and DA agonists in these models are frequently similar, the neural mechanisms underlying these manifestations are apparently distinct. The latter indicate that similar manifestations of abnormal behavior induced by muscarinic antagonists and DA agonists may represent different phenomena, and therefore may model different aspects of schizophrenic psychoses. Antimuscarinic-induced behavioral aberrations may model attentional abnormalities associated with alterations in muscarinic transmission/receptors seen in schizophrenia, which may be linked to positive symptoms as well as to cognitive impairments seen in this disorder.

On the other hand, not many attempts have been made to develop animal models based on cholinergic insult or cholinergic pharmacological manipulation, which would mimic cognitive symptoms of schizophrenia and show predictive validity for treatments considered effective for these symptoms. “Cholinergic models” of schizophrenia should provide a useful tool for the screening of both antipsychotic and pro-cognitive properties of drugs, and for allowing a differentiation between these actions of novel and/or known drugs. Moreover, “cholinergic models” may provide further insight into the basic neuropsychopharmacological mechanisms underlying schizophrenia symptom. The antimuscarinic LI model described here is, to the best of our knowledge, the first systematic attempt to establish a valid (anti)cholinergic behavioral model of schizophrenia, and is based on the extensive knowledge on LI as a psychological phenomenon and as a model of schizophrenia. However, this model is using an acute pharmacological manipulation, which allows screening of drugs and investigation of neuropsychopharmacological mechanisms, but does not allow the assessment of more chronic changes associated with cholinergic alterations in the brain. Thus, the development of

genetic or specific lesion-induced models that would mimic chronic cholinergic alterations and show predictive validity is highly desirable in order to promote the knowledge on the role of cholinergic dysfunction in schizophrenia, and its interplay with other neurotransmission systems in the brain.

Conflict of interest

None.

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