1. Introduction

A deficit in central cholinergic neurotransmission has been established as a core pathophysiological feature in Alzheimer’s disease. Thus, the inhibition of acetylcholinesterase is the most successful strategy for current symptomatic treatments for the disease. The acetylcholinesterase inhibitors used to treat Alzheimer’s disease patients are donepezil, rivastigmine, and galantamine. Galantamine is a selective and rapidly-reversible acetylcholinesterase inhibitor and also an allosterically potentiating ligand of neuronal nicotinic receptors (1). The drug interacts with the nicotinic receptor at binding sites separate from those for ACh and nicotinic agonists and acts specifically to enhance the activity (sensitize) of nicotinic receptors in the presence of ACh (2). This effect appears to be beneficial for the treatment of Alzheimer’s disease, in view of the previous findings that the severity of cognitive impairment in Alzheimer’s disease correlates with loss of nicotinic receptors (3, 4) and prolonged direct agonism for nicotinic receptors may cause desensitization rather than increased activation of the receptors (5).

Cholinergic alterations are also involved in several psychiatric disorders. There is growing clinical evidence that galantamine, currently used for the treatment of Alzheimer’s disease, may improve cognitive dysfunction and psychiatric illness in schizophrenia, major depression, bipolar disorder, and alcohol abuse. Since galantamine is a rather weak acetylcholinesterase inhibitor, but has additional allosteric potentiating effects at nicotinic receptors, it affects not only cholinergic transmission but also other neurotransmitter systems such as monoamines, glutamate, and γ-aminobutyric acid (GABA) through its allosteric mechanism. It is likely that these effects may result in further beneficial effects. To understand the underlying mechanism for the clinical effectiveness of galantamine, neuropharmacological studies have been performed in animal models of several psychiatric disorders. These studies suggest that not only the nicotinic receptor–modulating properties but also the muscarinic receptor activation contribute to the antipsychotic effect and improvement of cognitive dysfunction by galantamine. This review summarises the current status on the pharmacology of galantamine, focusing on its effect on neurotransmitter release and pharmacological studies in animal models of psychiatric disorders.

Keywords: galantamine, psychiatric disorder, acetylcholinesterase, nicotinic and muscarinic receptors, neurotransmitter release
psychiatric disorders. In schizophrenia, alterations in nicotinic and muscarinic receptor subtypes may contribute to cognitive impairment and choline acetyltransferase activity in the parietal cortex is negatively correlated with the severity of such cognitive impairment (6 – 8). Decreased muscarinic receptor availability (binding activity) in the rostral and dorsolateral and prefrontal cortices is associated with both bipolar disorder and major depressive disorder (9, 10). On the other hand, genetic variation in the CHRNA5 gene, which encodes the α5 subunit of the nicotinic receptors, affects mRNA levels and is associated with risk of alcohol dependence (11). These observations suggest that deficits in the cholinergic system including nicotinic receptors are implicated in the pathophysiology of psychiatric disorders as well as Alzheimer’s disease.

It has been shown that adjunctive galantamine can improve negative and cognitive symptoms in schizophrenia (12 – 17), although negative results are also reported (18, 19). Moreover, galantamine improves mood in some patients with major depression (20) or hastens the antidepressant treatment response in patients with late-life depression (21). In this relation, Elgamal et al. (22) demonstrated using quantitative electroencephalography that galantamine reduced absolute power in the beta band in the left central, left posterior, and right posterior regions of patients with major depressive disorder, suggesting a sign of brain activation. In bipolar disorders, galantamine reduces manic symptoms (23) and improves cognitive dysfunction (24 – 26). Improvement of cognitive dysfunction by galantamine is also observed in cocaine users (27). In addition, Mann et al. (28) reported that galantamine reduced the alcohol consumption of relapsed patients with alcohol dependence. These findings suggest the therapeutic potential of galantamine in psychiatric disorders.

To understand the underlying mechanism for the clinical effectiveness of galantamine, neurochemical and behavioral studies have been carried out. Galantamine affords neuronal protection against the cytotoxic effects of glutamate, trophic factor deprivation, hypoxia, and β-amyloid via its action on nicotinic receptors (29). Moreover, galantamine enhances neurotransmitter release (30 – 34) and it improves memory performance in animal models (29). These effects may contribute to the clinical effects of galantamine. Several excellent reviews on the clinical and pharmacological effects of galantamine have been published (6, 29, 35 – 37). This review focuses on recent studies on the effects of galantamine on neurotransmitter release and its behavioral effects in animal models of psychiatric disorders.

2. Effects of galantamine on neurotransmitter release

Since nicotinic receptors are located not only on cholinergic terminals, but also on the terminals of non-cholinergic neurons, the activation of nicotinic receptors stimulates ACh release as well as the release of other neurotransmitters (38). Indeed, systemic administration of nicotine stimulates in vivo release of dopamine, noradrenaline, 5-HT, and glutamate in several brain regions including the prefrontal cortex, striatum, nucleus accumbens, and hippocampus (39 – 41). Therefore, the allosteric modulating action of galantamine on nicotinic receptors could enhance the release of these neurotransmitters in the brain (Table 1).

2.1. ACh

Atypical, but not typical, antipsychotics increase ACh release in the prefrontal cortex and hippocampus (42, 43). The finding suggests that the increased ACh contributes to the ability of improving cognition and negative symptoms (44, 45). It is also likely that the increased cholinergic neurotransmission is responsible for the clinical effects of galantamine. In this line, Roman et al. (46, 47) reported that galantamine increased the [3H]ACh overflow in rat cortical synaptosomes and striatal slices. Moreover, Di Cara et al. (30) reported that systemic administration of galantamine (3 mg/kg) increased the extracellular ACh levels in the hippocampus and frontal cortex of rats. We have recently found that galantamine and donepezil increased the ACh levels in the prefrontal cortex of mice to similar extents (34), although donepezil was 3 – 15 times more potent than galantamine at inhibiting brain acetylcholinesterase (48). We also showed that addition of neostigmine, a cholinesterase inhibitor, during perfusion inhibited donepezil-induced increase in ACh levels much higher than the galantamine-induced increase. These observations suggest that mechanisms other than acetylcholinesterase inhibition are also involved in the galantamine-induced increases in ACh levels in the prefrontal cortex. In this connection, we found that galantamine increased extracellular dopamine concentrations in the prefrontal cortex, and the effect of galantamine on ACh levels was partially blocked by the dopamine-D1-receptor antagonist SCH23390 (34). Therefore, a dopamine-D1 receptor–mediated mechanism may contribute to galantamine-induced increase in prefrontal ACh levels (Fig. 1).

2.2. Dopamine

Zhang et al. (49) first showed that galantamine increased dopamine release from nerve terminals in mouse striatal slices. Schilström et al. (32) found using in vivo
Table 1. Galantamine-induced modulation of neurotransmitter release

<table>
<thead>
<tr>
<th>Region</th>
<th>Species</th>
<th>Treatment</th>
<th>Experiments</th>
<th>Effect</th>
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<tr>
<td>ACh</td>
<td>Prefrontal cortex synaptosomes</td>
<td>Rat</td>
<td>0.4 μM Nicotinic receptor–mediated [³H]ACh release</td>
<td>↑</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Striatal slices</td>
<td>Rat</td>
<td>0.001 – 100 μM Electrically stimulated [³H]ACh release</td>
<td>↑ (10, 100 μM)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>Rat</td>
<td>0.04 – 0.63 mg/kg, s.c. In vivo release</td>
<td>↑ (0.16, 0.63 mg/kg)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Frontal cortex</td>
<td>Rat</td>
<td>0.0025 – 0.63 mg/kg, s.c. In vivo release</td>
<td>↑ (≥0.01 mg/kg)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Prefrontal cortex</td>
<td>Mouse</td>
<td>1, 3 mg/kg, i.p. In vivo release</td>
<td>↑ (1, 3 mg/kg)</td>
<td>34</td>
</tr>
<tr>
<td>DA</td>
<td>Striatal slices</td>
<td>Mouse</td>
<td>0.1 – 100 μM In vitro release</td>
<td>↑ (0.4 μM), ↓ (10, 100 μM)</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Prefrontal cortex</td>
<td>Mouse</td>
<td>1, 3 mg/kg, i.p. In vivo release</td>
<td>↑ (1, 3 mg/kg)</td>
<td>34</td>
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<tr>
<td></td>
<td>Medial prefrontal cortex</td>
<td>Rat</td>
<td>0.1, 1 mg/kg, s.c. In vivo release</td>
<td>↑ (0.1 mg/kg)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Saline- or PCP-treated mice</td>
<td>Rat</td>
<td>0.05 mg/kg, p.o. In vivo release</td>
<td>±</td>
<td>50, 51</td>
</tr>
<tr>
<td></td>
<td>Saline- or PCP-treated mice combined with RIS</td>
<td>Rat</td>
<td>0.05 mg/kg, p.o. In vivo release</td>
<td>↑</td>
<td>50, 51</td>
</tr>
<tr>
<td></td>
<td>METH-treated mice</td>
<td>Rat</td>
<td>3 mg/kg, p.o. In vivo release</td>
<td>↑</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Nucleus accumbens</td>
<td>Rat</td>
<td>3 mg/kg, s.c. In vivo release</td>
<td>±</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Nucleus accumbens</td>
<td>Rat</td>
<td>3 mg/kg, s.c. Nicotine (0.025 – 0.065 mg/kg, i.v.)-stimulated in vivo release</td>
<td>±</td>
<td>33</td>
</tr>
<tr>
<td>NA</td>
<td>Hippocampal slices</td>
<td>Rat</td>
<td>0.5 – 3 μM Nicotinic (1, 5 μM)-induced [³H]NA release</td>
<td>↑</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>Rat</td>
<td>3 mg/kg, s.c. In vivo release</td>
<td>±</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Prefrontal cortex</td>
<td>Rat</td>
<td>3 mg/kg, s.c. Nicotine (0.025 – 0.065 mg/kg, i.v.)-stimulated in vivo release</td>
<td>↑</td>
<td>33</td>
</tr>
<tr>
<td>5-HT</td>
<td>Prefrontal cortex</td>
<td>Mouse</td>
<td>1, 3 mg/kg, i.p. In vivo release</td>
<td>±</td>
<td>34</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Hippocampal slices</td>
<td>Rat</td>
<td>0.1 – 10 μM Field stimulation–induced EPSC amplitude</td>
<td>↑ (0.5 – 3 μM)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Hippocampal neurons</td>
<td>Rat</td>
<td>1 μM AMPA, kainate or NMDA receptor–stimulated EPSC amplitude</td>
<td>±</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Cortical neurons</td>
<td>Rat</td>
<td>1 μM ACh-induced EPSC amplitude and frequency</td>
<td>±</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Prefrontal cortex</td>
<td>Rat</td>
<td>3 mg/kg, i.p. Kynurenic acid–induced decrease in in vivo release</td>
<td>↓</td>
<td>55, 56</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>Human</td>
<td>8 mg/day for 1 month and 16 mg/day for additional 3 months Metabolite concentrations measured by ¹H MRS</td>
<td>↑ (Glutamate and the ratio of glutamate to creatine)</td>
<td>61</td>
</tr>
<tr>
<td>GABA</td>
<td>Hippocampal slices</td>
<td>Rat</td>
<td>1 μM Field stimulation– or ACh-induced IPSC amplitude</td>
<td>↑</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Cerebral cortical slices</td>
<td>Human</td>
<td>1 μM ACh-induced IPSC amplitude</td>
<td>↑</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Cortical neurons</td>
<td>Rat</td>
<td>1 μM ACh-induced IPSC amplitude and frequency</td>
<td>±</td>
<td>54</td>
</tr>
</tbody>
</table>

single unit recordings that systemic administration of galantamine at low doses of 0.01 and 0.1 mg/kg increased firing activity of dopaminergic cells in the ventral tegmental area of anesthetized rats. This study suggests that galantamine activates midbrain dopaminergic neurons via nicotinic α7-receptor stimulation, since the effect of galantamine is prevented by the non-selective nicotinic antagonist mecamylamine and the selective α7 nicotinic-receptor antagonist methyllycaconitine, but not by the muscarinic antagonist scopolamine. In addition, a microdialysis study demonstrated that galantamine at doses of 0.1 mg/kg, but not 1 mg/kg, significantly increased extracellular dopamine levels in the medial prefrontal cortex of rats (32). Wang et al. (50, 51) showed that co-administration of galantamine and risperidone, an atypical antipsychotic drug, at their non-effective doses of 0.05 mg/kg caused significant increases in the extracellular dopamine levels in the medial prefrontal cortex of mice (32). Wang et al. (50, 51) showed that galantamine increased extracellular levels of acetylcholine and dopamine in the prefrontal cortex. AChE: acetylcholinesterase, DA: dopamine, D1R: dopamine-D1 receptor, Glu: glutamate, KcNQ2: small conductance Ca2+-activated K+ (SK) channel, nAChR (α7): α7-subunit containing nicotinic receptor, nAChR (β2): β2-subunit containing nicotinic receptor, NBM: nucleus basalis magnocellularis, NMDAR: N-methyl-D-aspartate receptor, SNc: substantia nigra pars compacta, VTA: ventral tegmental area.

2.3. Noradrenaline

Dajas-Bailador et al. (53) first reported that galantamine (1 μM) significantly increased [3H]noradrenaline release from hippocampal slices and it (0.5 – 3 μM) potentiated nicotine-evoked [3H]noradrenaline release. An in vivo microdialysis study showed that galantamine with nicotine at ineffective doses increased noradrenaline release, although galantamine (3 mg/kg) alone did not affect the release in the hippocampus of rats (33). This study also demonstrated that galantamine enhanced nicotine-stimulated noradrenaline release.

2.4. 5-HT

Galantamine does not affect 5-HT release in the brain. We observed that systemic administration of galantamine at doses of 1 and 3 mg/kg did not affect the extracellular 5-HT levels in the prefrontal cortex of mice (34).
2.5. Glutamate and γ-aminobutyric acid (GABA)

There are few reports on the examination of the effect of galantamine on in vivo release of glutamate and GABA in the brain, but some studies using the patch-clamp technique demonstrate that galantamine facilitates the excitatory and inhibitory synaptic transmission in brain slices and primary neurons.

In rat hippocampal slices, galantamine (0.5 – 3 μM) potentiated the field stimulation–induced excitatory postsynaptic current (EPSC) amplitude, indicating the enhancement of glutamatergic synaptic neurotransmission (31). Galantamine-induced facilitation of glutamatergic neurotransmission was abolished in the presence of FK1, the anti-nicotinic receptor antibody. Therefore, it is likely that galantamine acts as a nicotinic allosteric potentiating ligand. On the other hand, galantamine did not affect the α7 nicotinic receptors, or kynurenic acid, an astrocyte-derived metabolite that inhibits α7 nicotinic receptors, or kynurenine, a bioprecursor of kynurenic acid, in the prefrontal cortex of rats (55, 56), although galantamine alone did not affect the basal extracellular glutamate levels. Since kynurenic acid levels in the brain and cerebrospinal fluid of schizophrenic patients are elevated (57, 58) and kynurenine acid disrupts sensorimotor gating and cognitive processes (59, 60), endogenous kynurenic acid may be involved in the pathophysiology of schizophrenia. Thus, it is likely that the reversal of kynurenic acid–induced suppression of glutamatergic neurotransmission by galantamine may be responsible for its clinical effect in schizophrenia. Penner et al. (61) have more recently showed using proton magnetic resonance spectroscopy (1H MRS) that four months of galantamine treatment, which consisted of an 8 mg daily dose for the first month and a 16 mg daily dose for the remaining three months, increased absolute glutamate levels and the ratio of glutamate to creatine in the right hippocampus of patients with Alzheimer’s disease. They also demonstrated that the changes were associated with the increased cognitive performance in patients.

Regarding the GABA-ergic transmission, Santos et al. (31) showed that galantamine (1 μM) potentiated the field stimulation or ACh-induced inhibitory postsynaptic current (IPSC) amplitude in rat hippocampal slices. Galantamine also potentiates ACh-induced IPSC amplitude via nicotinic receptors in human cerebral cortical slices. But, galantamine does not affect the ACh-induced IPSC amplitude and frequency in the primary cortical neurons (54).

3. Effects of galantamine on animal model of psychiatric disorders

ACh acts in many cognitive functions such as sensory information processing, attention, memory and learning. Most studies on galantamine appear to focus on the effect on cognitive or memory impairment in animal models of schizophrenia and other psychiatric disorders (Table 2).

3.1. Schizophrenia

Wang et al. (50, 51) examined the effects of galantamine alone and in combination with risperidone in a PCP-induced model. PCP induces psychotomimetic states in humans and rodents. Since PCP psychosis incorporates not only the positive symptoms but also the negative symptoms and cognitive dysfunction, PCP-treated animals have been proposed as a preclinical model of schizophrenia (62, 63). Galantamine significantly improved the impairment of social interaction (50) and of latent visuospatial learning and memory (51) in PCP-treated mice. Furthermore, co-administration of risperidone and galantamine at lower doses improved significantly the impairment, but not when administered alone. These results suggest that galantamine may be effective in treating the negative symptoms and cognitive dysfunction of schizophrenia and it may have a synergistic effect with risperidone. Co-administration of galantamine and risperidone also increased extracellular dopamine levels in the medial prefrontal cortex of PCP-treated mice (50, 51) (see above and Table 1). The synergistic behavioral effect was blocked by SCH 23390 and mecamylamine, but not by scopolamine. Mecamylamine also inhibited the combination-induced increase in dopamine levels. Therefore, the combined effect of galantamine and risperidone may be mediated by activation of nicotinic receptor– and dopamine-D1 receptor–mediated neurotransmission.

The synergistic effect of galantamine is also demonstrated in the conditioned avoidance response test, an animal model of antipsychotic activity having a high predictive validity (64). Wiker et al. (65) reported that galantamine at doses of 5 mg/kg alone attenuated the conditioned avoidance response, and at lower doses (1 mg/kg) it potentiated typical antipsychotic raclopride–induced avoidance response in rats. In addition, adjunctive galantamine (1.25 mg/kg) also enhanced the antipsychotic-like effects of haloperidol and risperidone in the conditioned avoidance response test (66).

Prepulse inhibition (PPI) refers to the normal inhibi-
<table>
<thead>
<tr>
<th>Experiments</th>
<th>Species</th>
<th>Treatment</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Mouse</td>
<td>0.05 – 3 mg/kg, p.o.</td>
<td>Improved (0.3, 3 mg/kg)</td>
<td>50</td>
</tr>
<tr>
<td>PCP-induced social withdrawal</td>
<td>Mouse</td>
<td>GAL (0.05 mg/kg, p.o.) + RIS (0.05 mg/kg, p.o.)</td>
<td>Improved (synergistic effect)</td>
<td>50</td>
</tr>
<tr>
<td>PCP-induced impairment of latent visuospatial learning and memory</td>
<td>Mouse</td>
<td>0.05 – 0.3 mg/kg, p.o.</td>
<td>Improved (0.3 mg/kg)</td>
<td>51</td>
</tr>
<tr>
<td>Social isolation-induced PPI deficits</td>
<td>Mouse</td>
<td>1, 3 mg/kg</td>
<td>Improved (3 mg/kg)</td>
<td>71, 75</td>
</tr>
<tr>
<td>Apomorphine-induced PPI deficits</td>
<td>Mouse</td>
<td>1, 3 mg/kg</td>
<td>Improved (3 mg/kg)</td>
<td>34, 71</td>
</tr>
<tr>
<td>Apomorphine-induced PPI deficits</td>
<td>Rat</td>
<td>0.3 – 3 mg/kg, s.c.</td>
<td>Improved (3 mg/kg)</td>
<td>70</td>
</tr>
<tr>
<td>MK-801–induced PPI deficits</td>
<td>Mouse</td>
<td>1, 3 mg/kg</td>
<td>No effect</td>
<td>71</td>
</tr>
<tr>
<td>MK-801–induced PPI deficits</td>
<td>Rat</td>
<td>0.3 – 3 mg/kg, s.c.</td>
<td>No effect</td>
<td>70</td>
</tr>
<tr>
<td>MK-801–induced hyperlocomotion and deficits in spatial reversal learning and in contextual and cued memory</td>
<td>Mouse</td>
<td>0.25 – 1 mg/kg, s.c.</td>
<td>No effect</td>
<td>100</td>
</tr>
<tr>
<td>Conditioned avoidance response (CAR)</td>
<td>Rat</td>
<td>0.1 – 5 mg/kg, s.c.</td>
<td>Suppression of CAR (5 mg/kg)</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>1.25 – 5 mg/kg, s.c.</td>
<td>Potentiation of raclopride-induced avoidance response (1, 5 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Mouse</td>
<td>3 mg/kg, p.o.</td>
<td>Improved</td>
<td>81</td>
</tr>
<tr>
<td>METH-induced impairment of recognition memory</td>
<td>Mouse</td>
<td>3 mg/kg, p.o.</td>
<td>Improved</td>
<td>81</td>
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<tr>
<td>Amphetamine-induced psychotic-like behaviors</td>
<td>Monkey</td>
<td>0.1 – 1 mg/kg, s.c.</td>
<td>Inhibition of amphetamine-induced arousal, unrest, stereotypy (≥0.6 mg/kg)</td>
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<tr>
<td>Cocaine-induced behavioral sensitization</td>
<td>Mouse</td>
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<td>Inhibition of the expression of cocaine-induced locomotor sensitization</td>
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<td>Alcohol addiction</td>
<td>Rat</td>
<td>2.5 – 10 mg/kg, p.o.</td>
<td>Inhibition of ethanol preference in alcohol-preferring AA (Alko alcohol) rats (5, 10 mg/kg)</td>
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<tr>
<td>Alcohol-induced deficits in learning and memory</td>
<td>Rat</td>
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<td>Improvement of the impairment of the speed of learning, short-term memory and spatial orientation in prolonged alcoholic model</td>
<td>89</td>
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<tr>
<td>Depression</td>
<td>Mouse cortical neurons</td>
<td>0.01 – 10 μM</td>
<td>Increase in cell proliferation (≥0.5 μM)</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>5 mg/kg, i.p. for 14 days</td>
<td>Increase in cell proliferation in the SGZ and SVZ</td>
<td>95</td>
</tr>
<tr>
<td>BDNF</td>
<td>Rat</td>
<td>2.5 mg/kg, i.p.</td>
<td>Reversal of 152IgG-saporin-induced decrease in proBDNF protein levels</td>
<td>98</td>
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<tr>
<td>Anxiety</td>
<td>Rat</td>
<td>3, 6 mg/kg, s.c. for 12 days</td>
<td>No effect</td>
<td>99</td>
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tion of the startle response when a weak stimulus (the prepulse) immediately precedes an intense startling stimulus (the pulse). The PPI of startle is an operational measure of the pre-attentive filtering process known as sensorimotor gating, and abnormalities in pre-attentive information processing may be predictive of, or lead to, complex cognitive deficits in schizophrenia (67, 68). In addition, PPI performance may be related to cognitive processes in healthy males (69). Hohnadel et al. (70) reported that galantamine (3 mg/kg) improves PPI deficits induced by apomorphine, a non-selective dopamine-receptor antagonist, in rats. We have examined the effects of galantamine and donepezil on PPI deficits induced by apomorphine; MK-801, a non-competitive NMDA antagonist; and social isolation rearing in mice and observed that galantamine (3 mg/kg) improves apomorphine-induced PPI deficits in mice as well as rats (71). Interestingly, galantamine improved PPI deficits of isolation-reared mice, while donepezil did not. Clinical studies show that adjunctive galantamine can improve cognitive symptoms in schizophrenia (13 – 15, 17), while donepezil does not produce significant improvements (72 – 74). That is, the observation in isolation-reared mice appears to mimic the difference in the clinical effect between galantamine and donepezil. Therefore, it is likely that the isolation-reared PPI deficit model is useful for studies on the mechanism of the clinical effect of galantamine.

While the nicotinic receptor–modulating properties play a key role in the effects of galantamine, the muscarinic receptor activation contributes, at least partly, to the improvement of cognitive dysfunction. We have found that galantamine improves apomorphine- and isolation rearing–induced PPI deficits via an activation of the muscarinic receptors, especially M₁ (34, 75). In addition, Wadenberg et al. (66) recently reported that pretreatment with scopolamine, but not mecamylamine, completely reversed the enhancing effects of galantamine, when co-administered with haloperidol, in the conditioned avoidance response test. Although the inhibitory effect of galantamine on acetylcholinesterase is weak, microdialysis studies show that systemic administration of galantamine increases the extracellular ACh levels in mice (34) and rats (30). Thus, the effect of galantamine in increasing extracellular ACh levels may result in activation of muscarinic receptors.

### 3.2. Psychostimulant-induced behaviors (psychosis/cognitive deficits)

In nonhuman primates, the ability of galantamine to counteract d-amphetamine–induced behavioral effects was reported. There are several studies stating that drugs with antipsychotic activity antagonize d-amphetamine–induced behaviors in Cebus monkeys (76). Andersen et al. (77) showed that galantamine at doses of 0.6 and 1 mg/kg attenuated d-amphetamine–induced arousal, unrest, and stereotypy in Cebus monkeys.

Methamphetamine is a highly addictive drug of abuse, and chronic methamphetamine users show psychotic signs such as hallucinations and delusions, which are indistinguishable from paranoid schizophrenia (78, 79). Chronic use of methamphetamine also causes long-term cognitive deficits (80). Noda et al. (81) showed that galantamine (3 mg/kg) ameliorated the impairment of recognition memory in mice repeatedly pretreated with methamphetamine. In addition, mecamylamine and SCH 23390, but not scopolamine, blocked the ameliorating effect of galantamine on methamphetamine-induced memory impairment. Inhibition of extracellular signal–regulated kinase (ERK) by the microinjection of PD98059 into the prefrontal cortex also blocked the effect of galantamine. Thus, the improvement by galantamine may be mediated by activation of ERK signaling in a nicotinic receptor– and dopamine-D₁ receptor–mediated mechanism.

Repeated intermittent administration of cocaine can enhance the stimulating effect on locomotor activity, a phenomenon called behavioral sensitization. This behavioral model has been used extensively to analyze the neural modification associated with repeated cocaine exposure and withdrawal (82). Hikida et al. (83) reported that cholinergic cell ablation in nucleus accumbens increased the locomotive response and preference to cocaine. They (84) also showed that galantamine (1 mg/kg) inhibited the expression of cocaine-induced locomotor sensitization in mice. Although the mechanism for the effect of galantamine remains to be elucidated, this inhibition may be derived from increased ACh levels in the nucleus accumbens because donepezil also inhibited cocaine-induced locomotor sensitization and the depletion of ACh sources by cholinergic cell elimination markedly attenuated the inhibitory effect of donepezil.

### 3.3. Alcohol addiction (preference/memory impairment)

Alcohol is the most common drug of abuse. An increased health risk exists for all heavy drinkers, although only some of them develop addiction. Drugs reducing ethanol consumption would be of prophylactic benefit in such patients as they might be able to prevent alcohol-related diseases and block the developmental processes leading to addiction. Doetkotte et al. (85) reported that higher doses (5, 10 mg/kg) of galantamine inhibited ethanol intake in alcohol-preferring Alko alcohol (AA) rats. On the other hand, the previous work of Arendt et al. (86, 87) showed that prolonged alcohol intake in rats led to memory impairment and decreases in ACh content and
activities of choline acetyltransferase and acetylcholinesterase in the basal nucleus of Meynert. In addition, prolonged withdrawal from chronic ethanol consumption is associated with a decrease in β2-subunit containing nicotinic receptor availability in nonhuman primates (88). Iliev et al. (89) showed that administration of galantamine (2.5 mg/kg) to prolonged alcohol intake rats improved the speed of learning and short-term memory in the shuttle box test and the passive avoidance memory in the eight-arm radial maze.

3.4. Depression and anxiety

In preclinical studies, there is no report on the examination of the effect of galantamine on behavioral models of depression. However, the effects on neurogenesis and neurotrophic factor expression have been studied.

Neurogenesis occurs in early development and continues throughout adulthood in certain brain areas such as the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. Newly generated neurons in the adult mouse hippocampus may be integrated into the dentate granule cell circuitry and can display functional properties similar to those found in mature dentate granule cells (90). Thus, neurogenesis plays a crucial role in behavioral, physiological and cognitive processes (91, 92), and much attention has been focused on hippocampal neurogenesis in relation to the pathophysiology and treatment of depression (93, 94). Jin et al. (95) investigated the effect of galantamine on neurogenesis, measured by labeling newborn cells with bromodeoxyuridine (BrdU), in mouse cerebral cortical cultures in vitro and in the SGZ and SVZ of mice in vivo. Galantamine (0.01 – 10 μM) increased basal levels of BrdU incorporation into cortical cultures in a concentration-dependent biphasic manner. A maximally effective concentration was 0.5 μM. Galantamine (2.5 mg/kg) for 14 days also produced increases in the number of BrdU-labeled cells in both the SGZ and SVZ, indicating enhanced cell proliferation.

Brain-derived neurotrophic factor (BDNF) plays a key role in adult hippocampal neurogenesis, antidepressant treatment, and depressive-like behavior (96, 97). Gil-Bea et al. (98) have more recently found that the selective cholinergic immunotoxin, 192IgG-saporin, when administered into the third ventricle, impaired spatial acquisition memory in the Morris water maze test and decreased hippocampal protein levels of activity-regulated cytoskeleton-associated protein (Arc), an immediate-early gene, and proBDNF, the precursor of BDNF, leading to a diminished potential to consolidate new synapses. Galantamine (2.5 mg/kg) treatment improved acquisition performance with the retrieval of both Arc and proBDNF.

Fig. 2. Cholinergic dysfunction in psychiatric disorders and the possible mechanism for the beneficial effect of galantamine.
levels in $^{102}$IgG-saporin–treated rats. This study also showed that activation of muscarinic, but not nicotinic, receptors caused a rapid induction of Arc and BDNF production in hippocampal primary neurons. These findings imply that galantamine regulates synthesis of Arc and BDNF by activation of muscarinic receptors and finally promotes synapse consolidation and learning ability.

Hernandez et al. (99) performed light/dark preference experiments to evaluate the effects of galantamine on motor function and anxiety levels that might influence memory-related behaviors. However, daily treatment with galantamine (3, 6 mg/kg per day) for 12 days did not affect the general locomotor activity and anxiety-related behaviors of the aged rats.

4. Conclusion

In addition to Alzheimer’s disease, a deficit in cholinergic function has been identified in schizophrenia, major depression, bipolar disorder, and alcohol abuse. Current evidence suggests that galantamine may have a potential to provide the beneficial effects on these diseases, although further clinical trials with larger samples will be required. Galantamine, like donepezil, is a selective and rapidly-reversible acetylcholinesterase inhibitor and also acts as an allosterically potentiating ligand of nicotinic receptors. This action contributes to not only the neuronal protection against several neurotoxic stimuli but also enhancement of neurotransmitter release such as dopamine, noradrenaline, glutamate, and GABA. The latter effects of galantamine may be the basis for the improvement of abnormal behaviors in animal models of psychiatric disorders. Additionally, muscarinic receptor activation through increased brain ACh levels appears to mediate in part, anti-psychotic effects and the improvement through increased brain ACh levels appears to enhance of neurotransmitter release such as dopaminergic function has been identified in schizophrenia, major depression, bipolar disorder, and alcohol abuse. Current evidence suggests that galantamine may have a potential to provide the beneficial effects on these diseases, although further clinical trials with larger samples will be required. Galantamine, like donepezil, is a selective and rapidly-reversible acetylcholinesterase inhibitor and also acts as an allosterically potentiating ligand of nicotinic receptors. This action contributes to not only the neuronal protection against several neurotoxic stimuli but also enhancement of neurotransmitter release such as dopamine, noradrenaline, glutamate, and GABA. The latter effects of galantamine may be the basis for the improvement of abnormal behaviors in animal models of psychiatric disorders. Additionally, muscarinic receptor activation through increased brain ACh levels appears to mediate in part, anti-psychotic effects and the improvement of cognitive dysfunction by galantamine. Taken together, it is likely that galantamine may offer a unique therapeutic profile in psychiatric disorders (Fig. 2).

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