Drug targets for cognitive enhancement in neuropsychiatric disorders

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Review

Drug targets for cognitive enhancement in neuropsychiatric disorders

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ABSTRACT

The investigation of novel drug targets for treating cognitive impairments associated with neurological and psychiatric disorders remains a primary focus of study in central nervous system (CNS) research. Many promising new therapies are progressing through preclinical and clinical development, and offer the potential of improved treatment options for neurodegenerative diseases such as Alzheimer's disease (AD) as well as other disorders that have not been particularly well treated to date like the cognitive impairments associated with schizophrenia (CIAS). Among targets under investigation, cholinergic receptors have received much attention with several nicotinic agonists ($\alpha 7$ and $\alpha 4\beta 2$) actively in clinical trials for the treatment of AD, CIAS and attention deficit hyperactivity disorder (ADHD). Both glutamatergic and serotonergic (5-HT) agonists and antagonists have profound effects on neurotransmission and improve cognitive function in preclinical experiments with animals; some of these compounds are now in proof-of-concept studies in humans. Several histamine H3 receptor antagonists are in clinical development not only for cognitive enhancement, but also for the treatment of narcolepsy and cognitive deficits due to sleep deprivation because of their expression in brain sleep centers. Compounds that dampen inhibitory tone (e.g., GABA$_A$ $\alpha 5$ inverse agonists) or elevate excitatory tone (e.g., glycine transporter inhibitors) offer novel approaches for treating diseases such as schizophrenia, AD and Down syndrome. In addition to cell surface receptors, intracellular drug targets such as the phosphodiesterases (PDEs) are known to impact signaling pathways that affect long-term memory formation and working memory. Overall, there is a genuine need to treat cognitive deficits associated with many neuropsychiatric conditions as well as an increasingly aging population.

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Contents

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1. Introduction

Research on and development of novel therapeutic agents that improve cognitive function continues to receive much attention, not only because of the cognitive decline inherent to an aging population, but also because of the many neuropsychiatric conditions that have associated cognitive impairments with little or no viable treatment options (e.g., CIAS and Down syndrome) (Fig. 1). Cognition is a highly complex CNS function that includes attention, learning, memory and executive processes. Individual diseases may involve one specific impairment (e.g., attention in ADHD) or show global cognitive impairment (e.g., schizophrenia). As there is no consensus on optimal disease-relevant drug targets, many promising approaches are under study. These include research on drugs that enhance neurotransmission (e.g., acetylcholinesterase inhibitors; AChEIs), stimulate or inhibit key brain receptors (e.g., nicotinic agonists and 5-HT$_6$ receptor antagonists) and activate intracellular signaling cascades (e.g., PDE inhibitors). In addition, resurgence in the interest of herbal or naturally occurring nootropic agents (e.g., Ginko biloba) has emerged in recent years; this approach, however, is outside the scope of the present review.

Although many diseases are characterized by cognitive deficits or decline, treatments targeting AD populations have been the most consistently investigated. Nevertheless, the current list of approved cognitive enhancing drugs for AD is not long and traditionally has been focused on inhibiting the hydrolysis of acetylcholine (ACh) into acetate and choline by targeting acetylcholinesterase (AChE). Increasing ACh in the synapse can stimulate cholinergic receptors and promote enhanced memory function. Tacrine was the first approved AChEI in the early 1990s; second generation AChEIs such as donepezil and rivastigmine were introduced a few years later. Galantamine acts as an AChEI yet also has nicotinic α7 positive allosteric modulatory (PAM) properties that may be advantageous over standard therapies. Although AChEIs can temporarily delay the symptomatic progression of cognitive decline in AD, their effects are modest. In addition, with ACh present both centrally and peripherally, AChEIs produce troubling side effects such as gastrointestinal disturbances, bradycardia and excessive salivation that are associated with an action on peripheral muscarinic cholinergic receptors. These adverse effects (Bymaster et al., 2003) are often dose limiting and theoretically can interfere with a therapeutic benefit. Newer generation AChEIs (e.g., NP-0361) as well as modifications to existing treatments (e.g., physostigmine) are currently in various stages of clinical development.

Latrepirdine (Dimebolin), a drug marketed as an antihistamine for over 25 years, showed promise as a cognitive enhancing agent in a Phase II trial in mild to moderate AD patients (Sabbagh and Shill, 2010). In addition to its antihistamine activity, this drug also exhibits AChEI and butyrylcholinesterase inhibitor properties, is an NMDA receptor antagonist and 5-HT receptor antagonist, and inhibits L-type Ca^{2+} channels (Wu et al., 2008). However, in a more recent Phase III multinational trial, latrepirdine failed to improve cognition or global function in mild-to-moderate AD (http://www.medivation.com/product-pipeline/dimebon). Continued investigation into latrepirdine's potential therapeutic activity in AD is ongoing in patients on background donepezil therapy and, in a separate Phase III, study in patients diagnosed with Huntington's disease.

In addition to AChEIs, memantine has been added to the list of available drugs to treat moderate to severe cognitive impairment in AD. Memantine is a moderate affinity antagonist at the NMDA receptor and appears to modulate glutamate neurotransmission in a manner that results in the resumption of normal signal transduction and restoration of cognitive processes. Currently, memantine is marketed solely as a cognitive enhancing agent as claims of neuroprotection have not been proven clinically. In addition to memory enhancing compounds, drugs that improve attention, such as methylphenidate and amphetamine, have been prescribed for over 40 years for conditions such as ADHD. Attention-modulating drugs traditionally have been classified as psychostimulants because these block the neuronal reuptake of both dopamine and norepinephrine. Recently added to this category of attention-enhancing drugs is atomoxetine, which inhibits the norepinephrine transporter, but is the first marketed non-stimulant ADHD medication. Together, the drugs identified above are now available to treat problems of cognition. Many others representing more diverse mechanisms are under close experimental study and will be discussed below.

2. General mechanisms underlying learning and memory

Determining the mechanisms involved in how the brain acquires, stores and retrieves memories is one of the greatest challenges in the field of neuroscience. Even a partial understanding of the phenomena underlying cognitive function may lead to treatments of mental disorders when faculties begin to fail in a disease state. Ramón y Cajal first proposed that repeated stimulation of neuronal networks would
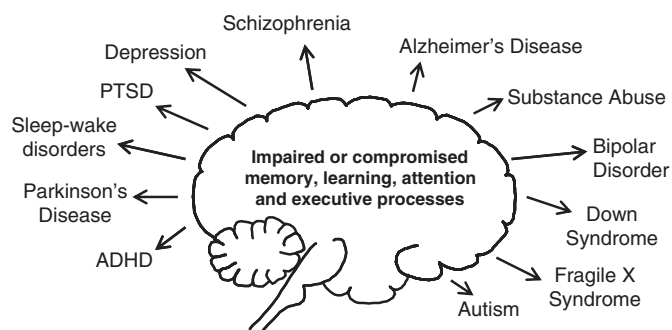

Fig. 1. Neurological and psychiatric illnesses linked to cognition impairment (mentioned in the current review).

strengthen synaptic connections and facilitate learning (Nestler et al., 2001). This idea was later championed by Donald Hebb in 1949, and confirmed using the gill withdrawal reflex of the invertebrate *Aplysia californica* undergoing a sensitization paradigm by Castellucci et al. (1970) and Kupfermann et al. (1970). Synaptic strengthening and plasticity occurs via changes in neurotransmission and alterations in signaling pathways. Much of the work that has aided the understanding of the molecular aspects of synaptic plasticity comes from studies using *in vitro* methods focused on long-term potentiation (LTP) in the hippocampus. Bliss and Gardner-Medwin (1973) demonstrated that high-frequency stimulation of axons within the perforant pathway of the hippocampus leads to enhanced postsynaptic responses in the dentate gyrus following subsequent stimulation. This enhanced response is input specific (i.e., occurring at stimulated, but not unstimulated, synapses), long-lasting (i.e., persisting for hours to weeks depending on induction protocol) and associative (i.e., coincident presynaptic and postsynaptic activation). Subsequently, LTP has been observed at many other synapses in the brain such as the lateral nucleus of the amygdala. Using the amygdala-dependent memory paradigm of conditioned fear provided *in vivo* support that LTP mechanisms may underlie long-term memory formation (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997).

Enhanced glutamate release from presynaptic neurons and subsequent activation of postsynaptic AMPA and NMDA receptors are critical for LTP induction. In particular, once the postsynaptic neuron is sufficiently depolarized, the Mg^{2+} block of the NMDA receptor is released and an influx of Ca^{2+} into the cell allows activation of Ca^{2+}/calmodulin kinase II and protein kinase C, as well as other second messenger systems (e.g., protein kinase A) that facilitate LTP. Changes in synaptic plasticity that occur for relatively short periods (e.g., hours) are generally considered to occur by alterations to existing proteins, for example, via phosphorylation. Longer-term changes in synaptic efficacy involve the synthesis of new proteins: activation of the transcription factor, cAMP responsive element binding protein (CREB), a critical mediator of LTP and long-term memory in multiple species (e.g., *Drosophila*, *Aplysia*, and mice) (*for review see* Frank and Greenberg, 1994). In addition, study of enhanced CREB function (and subsequently memory function) through small molecule approaches (e.g., PDE4 inhibitors) has been a long-standing interest of many scientists (Barco et al., 2003; Tully et al., 2003).

In addition to regulation of postsynaptic intracellular signaling cascades in mediating memory processes, many neurotransmitter systems influence learning and memory performance. As mentioned earlier, the glutamatergic system is intimately linked with LTP processes, and similar enhancements have been observed in *in vivo* learning and memory paradigms mediated through glutamate release and AMPA receptor activation. In addition, ACh is a critical mediator of learning and memory, and cholinergic neurons are particularly affected in diseases such as AD. Mildly enhanced dopamine transmission and activation of dopamine D1 receptors in the prefrontal cortex, in particular, has been described to mediate working memory function (Arnsten et al., 1994). In addition, whereas activation of certain GABA-ergic systems can impair memory, developing drugs that act as inverse agonists at the $GABA_A$ receptor have shown promise in enhancing memory function (Ballard et al., 2009).

Important to the development of any new drug is its efficacy evaluation in animal models. In particular, these preclinical assays can help to determine which cognitive domains are most likely to be affected by a particular mechanism of action, and ultimately will aid in the clinical study design. Whereas testing in naive animals is essential, it is important for new molecules to be characterized in the presence of existing therapies relevant to the targeted patient population in order to assess potential impact on efficacy (positive or negative). For example, some currently marketed therapies, e.g., antipsychotic drugs, have been reported to impair cognitive performance (Levin

and Rezvani, 2007). As this has the potential to mitigate any cognitive improvement produced by an investigational new drug, it is critical for the success of the clinical study to understand how the efficacy of a novel molecule may be impacted in patients on a background therapy prior to the initiation of the study. It is also important to evaluate drug efficacy in animal models of disease and not only in drug naïve animals to get information about drug action on a more predictive CNS background. Various disease models are available, although none is ideal. The possibilities, though, are many and are dependent on the pathology of interest. There are, for example, transgenic animals for AD, Rett and Down syndromes, animal models of ADHD, and procedures such as long-term impairment after treatment with NMDA antagonists for schizophrenia.

2.1. Cholinergic targets

ACh has long been recognized for its involvement in learning and memory, and degeneration of the cholinergic system is part of the pathophysiology of AD. ACh is synthesized in neurons located in the brainstem and basal forebrain that project to brain regions involved in regulating cognitive function such as the cerebral cortex and hippocampus. In addition, the basal ganglia is rich in cholinergic interneurons that mediate some forms of implicit memory. ACh exerts its effects at two receptor classes: (i) nicotinic receptors that are members of a ligand-gated ion channel receptor superfamily, and (ii) G-protein coupled muscarinic receptors. Both receptor classes are located centrally and peripherally, however, specific receptor sub-types within each class mediate cognitive function in the brain.

2.1.1. Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (nAChRs) are appropriately named because of their propensity to bind nicotine as well as the endogenous ligand, ACh. nAChRs are comprised of five subunits with binding sites located between subunits. Upon agonist binding, the ion channel opens and an influx of positive cations (e.g., calcium and sodium) enters causing neuronal depolarization. Whereas nAChRs are located throughout the body, the two most predominant receptors within the brain are heteropentameric α4β2nAChRs and homopentameric α7nAChRs. These two nAChR subtypes are highly localized within brain regions associated with cognitive function and have been most intensively studied for their role in mediating cognition. Early reports that nicotine administration improved performance in patients with diseases characterized by cognitive impairments (e.g., AD, schizophrenia, and ADHD) suggested a role for nAChRs in the pathophysiology of several disorders. To this end, drug discovery and development efforts targeted at the α4β2nAChR and the α7nAChR have received considerable attention.

Based on binding affinity, the α4β2nAChR is considered to have high (nM) and the α7nAChR low (μM) sensitivity to nicotine and ACh. Recently, the α4β2nAChR has been further classified based on the identification of two distinct stoichiometries in which this receptor subtype exists: $(α4)_2$ and $(β2)_3$ subunits (high sensitivity state) or $(α4)_3$ and $(β2)_2$ subunits (low sensitivity state) that are characterized by their binding affinity for ACh. The α4β2nAChR has been studied for its role in attention (Howe et al., 2010) and thus many drug development programs have targeted ADHD populations in addition to other disorders wherein attentional deficits are commonly observed (e.g., schizophrenia). α4β2nAChRs are localized in the cerebral cortex, hippocampus, ventral tegmentum and substantia nigra (Gotti et al., 2006). These are dopaminergic-rich brain regions and, thus, α4β2nAChRs are thought, in part, to mediate the rewarding properties of nicotine (Walters et al., 2006), a potential liability for drugs acting on this target.

As a treatment for smoking cessation, varenicline was the first nAChR agonist approved by the US Food and Drug Administration. Described as a partial α4β2nAChR agonist, it has subsequently been

found to have full agonist properties at the α7nAChR as well (Mihalak et al., 2006). Although there is some preclinical evidence that varenicline can improve recognition memory in rats (Rollema et al., 2009), it remains to be determined whether these results will translate into a similar effect in humans. Ongoing clinical trials in patients with AD and CIAS (www.clinicaltrials.gov; study identifiers NCT00744978 and NCT00523445) (Table 1) may help to elucidate this soon.

AstraZeneca and Targacept are collaborating on the research and development of several α4β2nAChR agonists for the treatment of cognitive impairment in ADHD, AD and schizophrenia. Ispronicline (AZD3480 and TC-1734) did not have a pronounced effect on cognition in patients with schizophrenia (HALO trial) or in mild-to-moderate AD patients (SIROCCO trial). Data from the latter trial were inconclusive in that the positive control (donepezil) did not differentiate from placebo. In mid-2009, AstraZeneca and Targacept announced they would continue evaluating ispronicline for an ADHD indication; Phase IIb studies were projected to begin in 2010. Evaluation of α4β2nAChR agonists for ADHD and AD indications is a rather competitive landscape (Table 1). In addition to ispronicline, AstraZeneca and Targacept are also pursuing a second molecule AZD1446 (TC-6683) for both diseases and were projected to initiate Phase IIa and Phase IIb trials, respectively, late in 2010. Abbott and Neurosearch partnered to develop ABT-894 (sofinicline) which completed a Phase II safety and efficacy study in adults with ADHD (www.clinicaltrials.gov; study identifiers NCT00429091). Similarly, Abbott has finished Phase IIb studies with ABT-089 (pozanicline) for both ADHD and AD. Amgen, Suven and Abbott with Neurosearch have α4β2nAChR PAMs in preclinical and early clinical development with no specific indications stated.

In addition to the pursuit of α4β2nAChR agonists, a great deal of effort has been devoted to developing agonist therapies targeted to the α7nAChR. α7nAChRs are localized almost exclusively in the brain with limited peripheral expression (Gotti et al., 2006), thus providing the potential for a reduced side effect profile. The α7nAChR is characterized by its high calcium permeability, which is greater than any of the other nAChRs, and its rapid desensitization upon agonist binding (Bertrand et al., 1993; Castro and Albuquerque, 1993, 1995; Seguela et al., 1993). Both ACh and choline bind to the α7nAChR. Activation of the α7nAChR produces pro-cognitive effects across multiple domains and species and may have neuroprotective properties (Kihara et al., 2001; Rezvani et al., 2009; Roncarati et al., 2009; Thomsen et al., 2010). The α7nAChR is also a central mediator of sensory gating, which is profoundly impaired in patients with schizophrenia. Moreover, abnormal P50 suppression (a measure of sensory gating) has been linked to genetic markers at the locus of the α7nAChR subunit gene on chromosome 15q13-14. Administration of nonselective α7nAChR agonists including tropisetron (also a 5-HT$_3$ receptor antagonist) and nicotine reverse the P50 auditory gating deficit observed in patients (Shiina et al., 2010; Simosky et al., 2002). These data, in part, have made the α7nAChR a drug target of great interest for treating CIAS.

GTS-21, an anabaseine derivative, is an α7nAChR partial agonist with weak α4β2nAChR antagonist properties that has been tested in clinical trials through Phase II for AD and CIAS (Table 1). Initial results showed improvements in cognitive function in healthy volunteers and in patients with schizophrenia using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) test, and it normalized the P50 auditory evoked potential (Kitagawa et al., 2003; Olincy et al., 2006). However, GTS-21 did not reverse cognitive impairments in patients in a subsequent study using the MATRICS scale (Freedman et al., 2008).

Roche is currently in Phase IIb with RG3487, a dual α7nAChR agonist and 5-HT$_3$ receptor antagonist (Wallace et al., 2011), as adjunctive therapy to donepezil for the treatment of AD. RG3487 (formerly known as MEM3454) monotherapy improved cognitive function using the Cognitive Drug Research test battery in healthy volunteers and in a Phase IIa mild-to-moderate AD population; it

recently completed a Phase II study in CIAS, and similar to GTS-21, did not improve cognitive endpoints as assessed by the MATRICS test battery. Roche also has a second molecule, RG4996, that has completed Phase I safety and tolerability studies; it is a selective α7nAChR agonist with no 5-HT$_3$ receptor antagonist properties. EnVivo Pharmaceuticals (EVP-6124) and Targacept (TC-5619) are both in Phase IIb studies with α7nAChR agonists for AD and CIAS. Like RG3487, EVP-6124 also has 5-HT$_3$ receptor antagonist properties.

Several groups have α7nAChR agonists and PAMs in various stages of preclinical and early clinical development. An α7nAChR PAM will still activate the ion channel, but limit the rapid desensitization characteristic of this receptor and avoid any direct interaction with nicotine in a smoking population. This latter issue may be of concern for a disease such as schizophrenia wherein up to 88% of the population is estimated to smoke (Moss et al., 2009). Xytis, with XY 4083, is the first company reporting a Phase I-ready α7nAChR PAM.

2.1.2. Muscarinic receptors

The five muscarinic receptor (mAChR) subtypes identified are classified based on differing intracellular signaling pathways. The M$_1$, M$_3$ and M$_5$ mAChRs couple to G$_q$ proteins, activate phospholipase C and subsequently mobilize intracellular calcium. M$_2$ and M$_4$ mAChRs couple to G$_{i/o}$ proteins and inhibit adenylate cyclase. Whereas all of the mAChR subtypes exist centrally, many are also localized peripherally with the M$_2$ and M$_3$ mAChRs being considered the primary systemic mediators of adverse effects associated with currently marketed AChEIs (Bymaster et al., 2003; Wess et al., 2007).

The M$_1$ mAChR is the predominant brain mAChR and is localized postsynaptically within the cortex, hippocampus, striatum and thalamus wherein it regulates the effects of ACh; this receptor received much initial attention as a potential drug target to improve learning and memory (Levey et al., 1991). Many companies have brought nonselective M$_1$ mAChR agonists (e.g., xanomeline and cevimeline) into clinical testing based on promising pro-cognitive effects from preclinical data. No M$_1$ mAChR agonist, however, has undergone successful development thus far, largely due to unacceptable safety profiles and minimal efficacy (Table 1). Most attribute this class failure to the absence of subtype selective molecules in that the orthosteric binding region of the mAChRs is rather highly conserved (Langmead et al., 2008). The M$_1$ mAChR allosteric site, which is not as well conserved across mAChRs, has garnered some support and provides an alternative approach for selectively activating the M$_1$ mAChR. Both M$_1$ mAChR allosteric agonists (e.g., TBPB and AC-42) and positive modulators (e.g., VU0119498 and VU0027414) have been described in detail previously [for review, see (Conn et al., 2009; Langmead et al., 2006)].

The M$_4$ mAChR is also widely expressed within the CNS and has received attention as a potential drug target for pro-cognitive activity, but has faced similar challenges as the M$_1$ mAChR with regard to selectivity. Thus, the study of allosteric activation and orthosteric/allosteric bitopic agonists is an area of active research. More recently, the identification of a small molecule (LY2033298) that acts as both a selective positive modulator and an agonist at the same allosteric M$_4$ mAChR site has provided an area of significant progress in the development of selective activators of the M$_4$ mAChR (Nawaratne et al., 2010).

Antagonism of the M$_2$ mAChR has also been investigated for potential pro-cognitive processes [for review, see (Langmead et al., 2008)]. M$_2$ mAChRs are located presynaptically in many brain regions including frontal and temporal cortices, and antagonism of this receptor elevates extracellular ACh concentrations (Billard et al., 1995) that may improve cognitive performance. In addition to the difficulty in developing selective molecules for the M$_2$ mAChR, another inherent limitation of targeting this receptor subtype is its high expression in the heart wherein antagonism may alter contraction force and parasympathetic control of heart rate.

T.L. Wallace et al. / Pharmacology, Biochemistry and Behavior 99 (2011) 130–145

Table 1
Drug targets for cognitive enhancement in clinical development. Source: Thomson Reuters Integrity. Key: PAM: positive allosteric modulator; NAM: negative allosteric modulator; AD: Alzheimer's disease; ADHD: attention deficit hyperactivity disorder; CIAS: cognitive impairment associated with schizophrenia; FXS: Fragile X syndrome; MCI: mild cognitive impairment; PD: Parkinson's disease; SZ: schizophrenia; TRD: treatment-resistant depression.

Compound name (code/generic/brand)	Target	Indication	Highest phase	Organization
Cholinergic targets: nACh and mACh receptors				
CP-526555-18/varenicline/Chantix; Champix	$\alpha4\beta2$ partial agonist $\alpha7$ full agonist	AD; CIAS	Launched 2006 for smoking cessation	Pfizer[a]
TC-1734; AZD-3480/ispronicline	$\alpha4\beta2$ agonist	AD; ADHD; MCI	II	AstraZeneca; Targacept[a]
TC-6683; AZD-1446	$\alpha4\beta2$ agonist	AD; ADHD	II	AstraZeneca; Targacept[a]
ABT-894/sofinicline	$\alpha4\beta2$ agonist	ADHD	II	Abbott[a]; NeuroSearch[a]
A-87089; ABT-089/pozanicline	$\alpha4\beta2$ partial agonist	AD; ADHD	II	Abbott[a]
ABT-560; ABT-PR2	$\alpha4\beta2$ agonist	Cognitive disorders	I	Abbott; NeuroSearch[a]
RG3487; R3487; MEM3454	$\alpha7$ partial agonist 5-HT$_3$ antagonist	AD; CIAS	II	Roche; Memory Pharmaceuticals[a]
MT-4666; EVP-6124	$\alpha7$ agonist 5-HT$_3$ antagonist	AD; CIAS	II	EnVivo Pharmaceuticals[a]; Mitsubishi Tanabe Pharma;
AZD-0328; AR-R23465XX	$\alpha7$ agonist	AD; CIAS	II	AstraZeneca[a]
TC-5619	$\alpha7$ agonist	AD; ADHD; CIAS	II	AstraZeneca; Targacept[a]
RG4996; R4996; MEM63908	$\alpha7$ partial agonist	AD	I	Roche; Memory Pharmaceuticals[a]
CP-810123	$\alpha7$ agonist	CIAS	I	Pfizer[a]
XY 4083	$\alpha7$ PAM	Cognitive disorders	I	Xytis
SB-202026A/sabcomeline/Memric	M$_1$ agonist	CIAS	II	GlaxoSmithKline[a]; Minster Pharmaceuticals
MCD-389	M$_1$ agonist	AD	I	Mithridion[a]
GSK-1034702	M$_1$ agonist	AD; CIAS	I	GlaxoSmithKline[a]
Glutamatergic targets: NMDA, AMPA and mGlu receptors				
Memantine/Namenda	NMDA antagonist	AD	Launched 2002	Merz and Lundbeck
EVT-101	NR2B antagonist	TRD	II	Evotec; Roche[a]
LY-451395	AMPA PAM	AD	II	Lilly[a]
CX-717	AMPA PAM	AD; ADHD	II	Biovail; Cortex[a]
CX-1739	AMPA PAM	AD; ADHD	I	Biovail; Cortex[a]
LY-2140023	mGlu2/3 agonist	SZ	II	Lilly[a]
ADX-71149	mGlu2 PAM	SZ	I	Ortho-McNeil-Janssen[a]; Addex[a]
RG-1578; R-1578	mGlu2/3 NAM	Depression	I	Roche[a]
NPL2009/fenobam	mGlu5 NAM	FXS	II	Ortho-McNeil-Janssen[a]; Neuropharm
AFQ056	mGlu5 NAM	FXS	II	Novartis[a]
STX107	mGlu5 NAM	FXS	I	Merck & co[a]; Seaside Therapeutics
Glycine targets				
D-serine	Glycine site agonist	CIAS; PD-cognitive impairment	III	NIMH; Hebrew University
RG1678	GlyT1 inhibitor	SZ	III	Roche[a]; Chugai[a]
SCH-900435; Org-25935	GlyT1 inhibitor	SZ	II	Merck & Co[a]; Organon[a]
PF-03463275	GlyT1 inhibitor	CIAS; SZ	II	Pfizer[a]
DCCCyB	GlyT1 inhibitor	SZ	I	Merck Sharp & Dohme[a]
R-231857	GlyT1 inhibitor	CIAS; SZ	I	Johnson & Johnson[a]
JNJ17305600	GlyT1 inhibitor	CIAS; SZ	I	NPS Pharmaceuticals[a]; Johnson & Johnson
AMG747	GlyT1 inhibitor	CIAS	I	Amgen
GABA$_A$ targets				
MK-0777	$\alpha2/3$ partial agonist	CIAS	II	Merck[a]; UCLA
L-830982	$\alpha2/3$ agonist	CIAS	II	Merck[a]
RG1662	$\alpha5$ inverse agonist	Cognitive disorders	I	Roche[a]
PDE targets				
PF-04447943	PDE9 inhibitor	AD	II	Pfizer[a]
PF-02545920; MP-10	PDE10 inhibitor	SZ	II	Pfizer[a]
Serotonergic targets				
PRX-03140	5-HT$_4$ partial agonist	AD	II	Nanotherapeutics; Epix Pharmaceuticals[a]
RQ-9; RQ-00000009	5-HT$_4$ partial agonist	AD	I	RaQualia[a]
Lu-AE-58054; SGS-518	5-HT$_6$ antagonist	AD	II	Lilly; Lundbeck;
SB-742457; GSK-742457	5-HT$_6$ antagonist	AD	II	GlaxoSmithKline[a]
SAM-531; PF-5212365; WAY-262531	5-HT$_6$ antagonist	AD; CIAS	II	Pfizer[a]
AVN-211	5-HT$_6$ antagonist	CIAS	II	Avineuro[a]
SUVN-502	5-HT$_6$ antagonist	AD	I	Suven Life Sciences[a]
SYN-114	5-HT$_6$ antagonist	Cognitive disorders	I	Roche[a]; Synosia Therapeutics
SYN-120	5-HT$_6$ antagonist	AD; CIAS	I	Roche[a]; Synosia Therapeutics
AVN-322	5-HT$_6$ antagonist	AD	I	ChemDiv[a]; Avineuro[a]
Histaminergic targets				
FUB-649; BF-2649/tiprolisant	H$_3$ inverse agonist/antagonist	CIAS	II	Biprojet[a]; Ferrer
GSK-239512	H$_3$ antagonist	MCI	II	GlaxoSmithKline[a]
S-38093	H$_3$ antagonist	AD	II	Motac Cognition; Servier[a]
SAR-110894	H$_3$ antagonist	AD	I	Sanofi-Aventis[a]
CEP-26401	H$_3$ antagonist	AD; CIAS	I	Cephalon[a]

[a] Company where compound was discovered.

2.2. Glutamatergic targets

Glutamate, the major excitatory neurotransmitter in the mammalian CNS, has long been known to play a major role in learning and memory processes. Glutamate activates both ionotropic (ligand-gated cation channels) and G-protein-coupled metabotropic receptors (Kew and Kemp, 2005). Fast excitatory transmission is mediated via ionotropic receptors whereas metabotropic glutamate receptors (mGluRs) modulate neuronal excitability and synaptic transmission. There is evidence that abnormalities of the glutamatergic system, particularly hypofunction of NMDA receptor signaling, are important for the underlying pathophysiology of schizophrenia. Moreover, dysfunction of the glutamatergic system has been implicated in disorders such as AD, ADHD and depression. The development of selective pharmacological tools has permitted exploration, primarily in animals, of the roles of different glutamatergic receptor subtypes on cognitive processes. In some cases, this has led to the clinical study of compounds acting at some of these molecular targets both in healthy volunteers and in patient populations (Table 1).

2.2.1. Ionotropic glutamate receptors

There are three main types of ionotropic receptors that have been named after the compounds which were originally identified as selective agonists for each receptor: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (kainate).

2.2.1.1. NMDA receptors. The NMDA receptor family is composed of seven subunits (NR1, NR2A–D, and NR3A–B) that are all products of separate genes. NMDA receptors are tetrameric structures likely composed of pairs of dimers such as an NR1 dimer in combination with an NR2x or NR3x dimer. For activation, the NMDA receptor requires two co-agonists, glycine and glutamate, binding at the NR1 and NR2 subunits, respectively. Blockade of NMDA receptors, for example by MK 801, leads to impairment of LTP and spatial learning and memory in rodents. However, as mentioned earlier, compounds that moderately block the NMDA receptor, such as memantine, may modulate excessive glutamate neurotransmission leading to improvements in cognition. Interestingly, compounds that are potent NR2B subunit selective antagonists do not impair spatial learning and memory in rodents (Guscott et al., 2003; Higgins et al., 2003; Willmore et al., 2002). This subunit is of interest with respect to cognition because over-expression of NR2B receptors in the mouse forebrain is associated with enhanced LTP and improved performance in learning and memory tasks, including spatial paradigms (Tang et al., 1999), which is still notable in aged transgenic mice (Cao et al., 2007). Further evidence for a role of NR2B receptors in hippocampal LTP and spatial learning has been supported by studies in aged rats (Clayton and Browning, 2001), anti-sense studies in young rats (Clayton et al., 2002) and a recent study in NR2B forebrain over-expressing transgenic rats (Wang et al., 2009).

In contrast, one study showed that Ro 25-6981, an antagonist of NR2B receptors, enhanced neurogenesis and spatial memory (Hu et al., 2008) and under certain test conditions some of these compounds, particularly CP-101,606 (traxoprodil), improved performance of working memory and attention tasks (Higgins et al., 2005). However, NR2B antagonists such as CP-101,606 and Ro 63-1908, also promoted impulsive-type responding in a five-choice serial reaction time task (Higgins et al., 2005). In humans, variability in the genes encoding the 2A and 2B subunits of the NMDA receptor (GRIN2A and GRIN2B) are associated with poorer performance in tests of episodic memory coupled with changes in hippocampal activity (de Quervain and Papassotiropoulos, 2006). There is clearly a role for NR2B receptors in cognitive processes although further work is required to understand the effects of positive and negative modulation of this receptor subtype on different cognitive domains and in different pathologies. Regarding

clinical studies, EVT-101 is a potent and selective NR2B subtype specific antagonist originating from Roche with an improved side effect profile compared to nonselective NMDA receptor antagonists. EVT-101, now with Evotec, was first in development for the treatment of AD and is now in Phase II for treatment-resistant depression (Table 1).

2.2.1.2. AMPA receptors. The AMPA receptor family is composed of four subunits, GluR1–4, which are products of separate genes. Alternative splicing of RNA gives rise to flip and flop variants of each subunit. Native AMPA receptors are believed to assemble as tetramers and are likely heteromeric. It has been shown that there are regional differences in the expression of AMPA receptor subunits throughout the rodent and non-human primate brain (Black, 2005) and different combinations of these subunits may result in functional diversity of the AMPA receptor (Ward et al., 2010). Glutamate-induced activation of postsynaptic AMPA receptors leads to an induction of LTP and, as mentioned previously, induces a change in synaptic morphology and strength that likely underlies learning and memory (Bliss and Gardner-Medwin, 1973).

Positive modulation of AMPA receptors may enhance cognition by modulating glutamatergic transmission, promoting synaptic plasticity and enhancing production of trophic factors such as brain derived neurotrophic factor (BDNF) (Lynch, 2004). Compounds from this class that enhance cognition in rodents include pyrroliddones (piracetam and aniracetam), benzothiazides (cyclothiazide), benzylpiperidines (CX-516 and CX-546) and biarylpropylsulfonamides (LY392098, LY404187, and LY503430) (Black, 2005; O'Neill et al., 2004). These compounds have no intrinsic activity yet enhance glutamate transmission via AMPA receptors by changing the rate of receptor desensitization. However, the activity of these compounds may depend on splice variant or subunit composition (Black, 2005).

CX516 was the first AMPA receptor positive modulator assessed for cognitive enhancement in schizophrenia. The compound was generally well tolerated but did not have an effect on cognition when combined with clozapine, olanzapine or risperidone (Goff et al., 2008b). CX516 had previously improved cognitive performance in healthy and elderly subjects but the lack of efficacy in the former study is thought to be due to weak potency and a short half-life in humans (Ward et al., 2010). Another modulator, LY451395, was studied in mild to moderate AD patients and although it was well tolerated there was no improvement in cognition after eight weeks of treatment (Chappell et al., 2007); this compound remains in clinical development for the treatment of AD (Table 1). Cortex Pharmaceuticals is conducting Phase II clinical trials with CX-717 for the treatment of cognition dysfunction associated with ADHD, AD and for the treatment of sleep deprivation.

2.2.2. Metabotropic glutamate receptors

The family of mGluRs consists of eight members classified by molecular and pharmacological properties into three main groups: group I (mGlu1 and 5), group II (mGlu2 and 3) and group III (mGlu4, 6, 7 and 8) (Kew and Kemp, 2005). Whereas group I mGlu receptors are primarily localized postsynaptically, group II and group III receptors are typically presynaptic and can regulate neurotransmitter release (Cartmell and Schoepp, 2000). Evidence for the therapeutic potential of mGluRs, particularly group I and II, for the treatment of CIAS, Fragile X syndrome, AD, Parkinson's disease and posttraumatic stress disorder has been reviewed previously (Gravius et al., 2010; Spooren et al., 2003).

2.2.2.1. Group I: mGlu1 and mGlu5 receptors. Both mGlu1 and mGlu5 receptors are expressed in neurons postsynaptically yet have different expression patterns in the brain suggesting that these receptors have different functions. mGlu1 receptors are expressed in the hippocampus, hypothalamus, thalamus, amygdala, basal ganglia, cerebellum and spinal cord (Fotuhi et al., 1993; Shigemoto et al., 1992). mGlu5

receptors are expressed in the cerebral cortex, hippocampus, amygdala, cortical areas (subiculum, entorhinal, cingulate and piriform cortices), basal ganglia, septum and olfactory bulb (Romano et al., 1995; Shigemoto et al., 1993). mGlu1 antagonists impair cognition in aversive learning paradigms such as the water maze and fear conditioning yet have equivocal effects in appetitively motivated tasks (see Lesage and Steckler, 2010 for review of data). Enhancement of glutamatergic transmission by positive allosteric modulation of mGlu1 receptors should result in enhanced cognition. However, to date there are no published reports on the effects of mGlu1 PAMs in learning and memory procedures. Like mGlu1, mGlu5 receptor antagonists also impair performance in aversively motivated cognition tests (Simonyi et al., 2010). The cognitive impairment noted with mGlu5 antagonists appears to be task- or context-dependent since not all cognitive tests are affected following blockade of this receptor.

mGlu5 receptor signaling has been implicated in the pathogenesis of fragile X syndrome (FXS) which is the leading inherited cause of mental retardation and the predominant identified cause of autism (Bear et al., 2004; Dolen and Bear, 2008). FXS is caused by transcriptional silencing of the FMR1 gene that encodes the fragile X mental retardation protein (FMRP). The hypothesis is that in the absence of FMRP, there is increased signaling via mGlu5 receptors leading to excessive protein synthesis and thus the clinical symptoms of the disorder, which include cognitive impairment (Bear et al., 2004; Dolen and Bear, 2008). Dolen et al. (2007) generated Fmr1 mutant mice with a 50% reduction in mGlu5 receptors and demonstrated that there was rescue of the Fmr1 phenotype, including reversal of the cognitive impairment. Therefore, mGlu5 receptor antagonists may provide an effective treatment for FXS. An initial evaluation has been completed with an mGlu5 receptor antagonist, fenobam, in an open-label single dose trial in twelve adult male and female patients with FXS (Berry-Kravis et al., 2009). There was a slight improvement in prepulse inhibition in six of the individuals and no significant adverse events were noted. Currently there are two clinical trials ongoing in FXS, with STX107 under evaluation for safety and tolerability in Phase I by Seaside Therapeutics and AFQ056 for safety and efficacy (behavior and cognition) in Phase II by Novartis (Table 1).

Positive allosteric modulation of mGlu5 receptors results in enhanced synaptic plasticity (Ayala et al., 2009) and cognition (Liu et al., 2008; Uslaner et al., 2009) in rodents. There is evidence for a functional interaction between mGlu5 receptors and NMDA receptors and this has been further substantiated by electrophysiological and behavioral studies with mGlu5 PAMs (Lecourtier et al., 2007; Liu et al., 2008; Rosenbrock et al., 2010; Stefani and Moghaddam, 2010; Uslaner et al., 2009). Therefore, mGlu5 PAMs may provide an alternative therapeutic approach for the treatment of CIAS.

2.2.2.2. Group II: mGlu2 and mGlu3 receptors. Of the group II mGlu receptors, mGlu3 is highly expressed in glia and mGlu2 is largely neuronal (Ohishi et al., 1994; Yokoi et al., 1996). *In situ* hybridization, immunohistochemical and autoradiography studies indicate that the mGlu2 receptor exhibits a regionally distinct expression pattern in adult brain with high levels in areas including the olfactory bulb, cerebellar cortex, caudate-putamen, cerebral cortex and the terminal fields of the perforant path input from the entorhinal cortex in the hippocampus (Mutel et al., 1998; Ohishi et al., 1993; Schaffhauser et al., 1998; Shigemoto and Mizuno, 2000). Considerable pharmacological evidence suggests that activation of group II mGlu receptors can markedly inhibit synaptic transmission (Anwyl, 1999; Cartmell and Schoepp, 2000) and thus can limit excitatory neurotransmission under conditions of high frequency repetitive activation (Kew et al., 2001; Scanziani et al., 1997). Furthermore, it has been shown in human hippocampal slices that group II mGlu receptor activity can modulate presynaptic glutamate release (Dietrich et al., 2002). It has been difficult to differentiate the actions of mGlu2 and mGlu3 due to

the lack of selective pharmacological tools. Nonetheless, modulation of group II mGlu receptors may have therapeutic potential for cognitive impairment associated with AD, depression and schizophrenia.

Early stage AD pathology is associated with neurodegeneration within the entorhinal cortex, hippocampus and associated circuitry such as the perforant pathway (Gomez-Isla et al., 1996). Results from morphological, electrophysiological and behavioral studies associate mGlu2/3 receptors in cognitive processes involving cortico-cortical connections within medial–temporal lobe structures predominantly at the perforant path inputs to the dentate gyrus (Higgins et al., 2004; Linden et al., 2006; Spinelli et al., 2005). The notion that mGlu2/3 receptor antagonists may rescue cognitive impairment in mild to moderate AD patients (Higgins et al., 2004) has not yet been studied clinically.

Preclinical evidence suggests that mGlu2/3 receptor antagonists induce biochemical and behavioral changes indicative of antidepressant activity (Pilc et al., 2008). It was recently shown that mGlu2/3 receptors are significantly increased in the prefrontal cortex (postmortem) in major depressive disorder (Feyissa et al., 2010). Since competitive mGlu2/3 receptor antagonists exhibit mild alerting, cognitive enhancing and neurogenesis properties in preclinical studies in rodents (Feinberg et al., 2005; Karasawa et al., 2006; Shimazaki et al., 2007), it was proposed that mGlu2/3 receptor antagonists would have an antidepressant profile with wakepromoting and cognition enhancing effects (Witkin et al., 2007). Currently, an mGlu2/3 negative allosteric modulator (NAM) from Roche, RG1578, is undergoing Phase I trials for depression (Table 1).

Regarding schizophrenia, interest in this indication was generated by data showing that the mGlu2/3 receptor agonist, LY354740, reversed the behavioral effects induced by PCP, including a working memory impairment (Moghaddam and Adams, 1998). Since then it has been shown that mGlu2/3 receptor agonists also attenuate cognitive impairments induced by neonatal PCP administration (Harich et al., 2007). In contrast, LY354740 was shown to worsen working memory, attention and spatial learning and memory when administered to naive rats and marmoset monkeys (Aultman and Moghaddam, 2001; Higgins et al., 2004; Spinelli et al., 2005). However, there are no reports of cognitive impairment in healthy volunteers. Moreover, there were modest effects of LY354740 in attenuating the working memory impairment induced by an NMDA receptor antagonist, ketamine, in healthy human volunteers (Krystal et al., 2005). Genetic studies have shown that a variation in the GRM3 genotype (encoding mGlu3) is associated with poorer performance on tests of hippocampal and prefrontal cortex function (de Quervain and Papassotiropoulos, 2006; Egan et al., 2004). A recent review suggested that the mGlu3 receptor may be the primary therapeutic target for the symptomatology of schizophrenia, including cognitive impairment (Harrison et al., 2008). However, a lack of selective mGlu3 receptor compounds currently precludes testing this hypothesis clinically. Cognition testing in schizophrenic patients is currently ongoing with LY-2140023, an mGlu2/3 receptor agonist from Lilly in Phase II trials (Table 1). Addex has an mGlu2 selective PAM, ADX-71149, in Phase I trials for schizophrenia.

2.3. Glycine targets

There is considerable evidence, ranging from pharmacological to imaging data, that support the notion that hypofunction of the NMDA receptor complex contributes to the pathophysiology of schizophrenia (Javitt, 1999, 2009). Importantly, genetics research over the past 5 years has provided additional data implicating an important role for glutamatergic signaling in schizophrenia, leading to the suggestion that psychosis is secondary to NMDA receptor hypofunction with a downstream effect on dopaminergic activity (Deutsch et al., 2001; Javitt and Zukin, 1991; Kegeles et al., 2000). Thus, new treatment

options for schizophrenia now focus on increasing NMDA receptor activity as this is expected to benefit patients by improving behaviors, particularly those mediated by the prefrontal cortex such as negative symptoms, working memory and executive functions. (Section 2.2.1.1 briefly describes the NMDA receptor complex.)

One way to modulate glutamatergic tone is to target directly or indirectly the glycine co-agonist site of the NMDA receptor. Glycine, via binding to the NMDA complex, enhances excitatory neurotransmission in cortical and hippocampal structures suggesting a role in cognition. Using glycine itself, however, is not a viable option as bioavailability and brain penetration markedly limit its utility. D-serine, which like glycine also binds as a co-agonist at the NR1 subunit, improved executive function in patients with schizophrenia when added to standard antipsychotic medication (Tsai et al., 1998). Similarly, it has been shown that treatment with agonists of the glycine site of the NMDA receptor like D-cycloserine improved the negative symptoms of patients with schizophrenia when given as adjunctive treatment to antipsychotics (Goff et al., 1995). D-Cycloserine, however, had limited effects on cognitive function in patients (Goff et al., 2008a; Otto et al., 2009).

Molecular, biochemical and behavioral data show that local concentrations of glycine in the forebrain are controlled by the action of the high-affinity glycine transporter type-1 (GlyT1) (Cubelos et al., 2005; Harsing, 2006). Therefore, NMDA receptor function can be enhanced by increasing glycine in the synaptic space of NMDA receptors by inhibition of GlyT1. Based on preclinical research, various cognitive domains appear improved by increased glycine levels. Social memory, for example, is improved in rodents after acute treatment with the GlyT1 inhibitor NFPS (Shimazaki et al., 2010). In this study, NFPS reversed the impairment induced by a time delay between session, and by MK-801. NFPS also reversed the impairment induced by MK-801 on object recognition (Karasawa et al., 2008), a model of short term working memory similar to the human CANTAB test, verbal recognition memory (Barnett et al., 2010). Another GlyT1 inhibitor, SSR504734, improved working memory in delayed alternation tasks in mice after sub-chronic treatment (Singer et al., 2009). In patients, the GlyT1 inhibitor, sarcosine, ameliorated symptoms of schizophrenia including cognitive impairment when added to risperidone, but not clozapine (Lane et al., 2005, 2006, 2010; Tsai et al., 1998). Moreover, PF-03463275 reversed impairment of working memory induced in non-human primates by pre-treatment with ketamine (Roberts et al., 2010). PF-03463275 is now in a clinical Phase II trial for CIAS. Other potent and selective GlyT1 inhibitors currently in clinical development are RG1678 from Roche, R-231857 from Johnson & Johnson and AMG747 from Amgen, the latter two for CIAS (Table 1).

2.4. GABA targets

GABA (γ-aminobutyric acid) is the principal inhibitory neurotransmitter in the mammalian CNS. The GABA$_A$ receptor is the predominant inhibitory neurotransmitter receptor in the CNS and has been widely used as a target for neuromodulatory drugs. Many compounds in clinical use as anxiolytics, sedatives, hypnotics or anti-epileptics increase GABA$_A$ receptor activation via the allosteric benzodiazepine (BZD) binding site on the receptor-chloride channel complex. Nonselective BZD receptor inverse agonists improved cognition in impairment paradigms in animals (Jensen et al., 1987; McNamara and Skelton, 1993; Venault et al., 1986), and in a few exploratory trials in healthy human volunteers (Duka et al., 1996). However, further clinical development of these nonselective compounds was prevented by anxiogenic effects seen in humans (Dorow et al., 1983) or concerns about convulsions.

GABA$_A$ receptors are pentamers mostly consisting of two α, two β and one γ subunits. Several gene products are available for each of the subunits giving rise to a large number of receptor variants. The importance of different α subunit subtypes has been elucidated by the generation of transgenic mice lacking the normal diazepam sensitivity of the α1, α2, α3 or α5 subunit (α4 and α6 are diazepam-insensitive). The results indicate that α1 is responsible for the sedative effects, α2 and perhaps α3 for the anxiolytic effects (Low et al., 2000; McKernan et al., 2000; Mohler, 2006; Rudolph et al., 1999) and α5 for the cognitive effects (Collinson et al., 2006; Crestani et al., 2002) of BZD receptor agonists.

Evidence that a disturbance in cortical GABA$_A$ receptor signaling underlies psychiatric disorders such as schizophrenia has been previously reviewed (Charych et al., 2009; Wassef et al., 2003), and it has been suggested that subtype selective compounds may provide a novel therapeutic approach. More specifically, it has been proposed that full positive allosteric modulators of α2, α3 or α5 may have therapeutic potential for the treatment of cognitive dysfunction associated with schizophrenia (Guidotti et al., 2005). In contrast, negative allosteric modulators of GABA$_A$ receptors may provide an effective therapy for the treatment of the cognitive deficits associated with disorders such as Down syndrome and neurofibromatosis (Fernandez et al., 2007; Rueda et al., 2008; Cui et al., 2008). The transgenic mouse model for Down syndrome, Ts65Dn, has been shown to have excessive inhibitory transmission in the hippocampus together with learning and memory deficits that can be attenuated by compounds that block activity at GABA$_A$ at sub-convulsant doses, such as picrotoxin (Fernandez et al., 2007) and pentylenetetrazole (Rueda et al., 2008). Increased inhibitory transmission is also associated with spatial learning deficits found in a mouse model of neurofibromatosis that were attenuated by treatment with picrotoxin at sub-convulsant doses (Cui et al., 2008). It is not yet known which receptor subtype is responsible for alleviating the cognitive impairment in these mouse models.

2.4.1. GABA$_A$ α2/3 receptors

A proof-of-concept trial was undertaken in a small sample of patients with schizophrenia with a relatively selective agonist at the α2 subtype, MK-0777 (or TPA023). MK-0777 induced improvements in only the delayed recall tests but also enhanced synchronization of cortical neuronal activity at gamma frequencies, which has been proposed to be of importance in higher cognitive processes (Lewis et al., 2008). Interestingly, MK-0777, at a dose-range which was consistent with the study in schizophrenia patients, significantly reversed a ketamine-induced deficit in a spatial working memory task in nonhuman primates (Castner et al., 2010). With these promising data, the University of California Los Angeles sponsored a Phase II trial with MK-0777 for CIAS (Table 1); however, it was recently reported that MK-0777 did not have a significant therapeutic effect (Buchanan et al., 2011). Since this compound is a relatively weak partial agonist at GABA$_A$ α2 receptors, Buchanan et al. proposed that one might need compounds with greater potency and selectivity for α2 and/or α3 to have a beneficial effect in patients.

2.4.2. GABA$_A$ α5 receptors

The preferential localization of α5 subunits is in the hippocampus (Fritschy and Mohler, 1995) and reduced expression of this subunit has been associated with facilitated cognition in hippocampal-dependent tasks in mice (Collinson et al., 2006; Crestani et al., 2002). Therefore, a BZD site ligand with inverse agonism selective for α5-containing GABA$_A$ receptors could enhance cognitive function without anxiogenic and pro-convulsant side effects. A number of compounds with binding or functional selectivity for α5-containing GABA$_A$ receptors have recently been synthesized; behavioral data from these compounds indicate that such a pharmacological profile can improve cognitive function without CNS-mediated adverse effects (Atack et al., 2006; Ballard et al., 2009; Collinson et al., 2006; Dawson et al., 2006; Savic et al., 2008). These compounds have been shown to positively modulate hippocampal-dependent tasks, such as spatial working memory in rodents (Atack et al., 2006; Ballard et al., 2009;

Collinson et al., 2006; Dawson et al., 2006; Savic et al., 2008), but there is also evidence for improved performance in a prefrontal cortex mediated executive function task in nonhuman primates (Ballard et al., 2009).

Since the density and pharmacology of α5 subunit-containing GABA$_A$ receptors are preserved in the hippocampus of AD patients (Howell et al., 2000), compounds were initially studied for their effectiveness in AD. A preliminary report showed that CP-457,920 (NGD 97-1), a partial α5 inverse agonist (α5IA), did not differ from placebo on cognition measures after 12 weeks of dosing (Tolar et al., 2004). However, the structure and *in vitro* properties of the compound have not been disclosed and so it is unknown whether an optimal combination of potency, efficacy, binding and functional selectivity was achieved. The functionally selective α5IA attenuated ethanol-induced impairment of word recall in healthy young volunteers (Nutt et al., 2007) and was well tolerated in a Phase I study in young and elderly volunteers (Atack, 2010). However, development was stopped due to renal toxicity (crystal formation) at high doses in preclinical toxicity studies in rats (Atack, 2010). MRK-016 was the back-up compound to α5IA; it was also well tolerated in young subjects but unfortunately poorly tolerated in elderly patients. Together with variable human pharmacokinetics, development of MRK-016 was stopped in Phase I (Atack et al., 2009). RG1662, an α5 selective inverse agonist from Roche, is currently undergoing Phase I clinical trials (Table 1).

2.5. PDE targets

cAMP and cGMP are crucial for cell signaling, synapse communication and synaptic plasticity. Consequently, regulation of cAMP and cGMP levels can be expected to impact cognitive function to some degree. Among the eleven known PDE families, five are of interest in the domain of cognition. These are PDE2, PDE4, PDE5, PDE9 and PDE10. PDE inhibitors block the metabolism of cAMP and/or cGMP resulting in increased CNS function particularly in areas of high enzyme localization such as the hippocampus, cortex, striatum and amygdala, supporting a role for these intracellular enzymes in cognitive processing.

2.5.1. PDE2

A limited number of pharmacological studies have been focused on the effects of PDE2 inhibitors in cognition. BAY60-7550, a selective PDE2 inhibitor, reversed an object memory deficit in rats on a special diet inducing low tryptophan in the CNS (van Donkelaar et al., 2008). With a dual effect on cAMP and cGMP, PDE2 inhibitors may affect both acquisition and consolidation in the memory process (Blokland et al., 2006).

2.5.2. PDE4

PDE4 is cAMP-specific and encoded by four different genes (PDE4A, PDE4B, PDE4C, and PDE4D). A single nucleotide polymorphism and haplotype association analysis in a large Finnish schizophrenia family sample demonstrated a link between the gene DISC1 and both PDE4B and PDE4D haplotypes (Tomppo et al., 2009). DISC1 is currently one of the most interesting candidate genes for mental illness and is associated with schizophrenia, bipolar disorder, major depression, and autism susceptibility (Camargo et al., 2008; Kilpinen et al., 2008; Palo et al., 2007) with growing evidence for a role in dendritic spine structures (Hayashi-Takagi et al., 2010). A similar genetic linkage between PDE4B and DISC1 was shown in a Japanese population (Numata et al., 2008).

With respect to preclinical research, there have been many studies performed with the non-selective PDE4 inhibitor, rolipram. In rats, rolipram has a beneficial role in spatial memory after ischemia and after treatment with scopolamine or NMDA antagonists (Reneerkens et al., 2009). Rolipram also improved inhibitory avoidance learning in

rodents treated with protein synthesis inhibitors. Contextual fear conditioning was improved by rolipram during retention in unimpaired rats and in transgenic mice for AD. Episodic-like memory measured via an object recognition task was improved by rolipram in rats, and it also reversed the disruptive effects of scopolamine. Some beneficial effects of rolipram on attentional performance were also described in Cynomolgus monkeys studied in an object retrieval task (Rutten et al., 2008). Another compound, RO-201724 was shown as having a beneficial effect on information processing in mice (Halene and Siegel, 2008). In general, however, development of PDE4 inhibitors has been compromised due to a number of target-related side effects including nausea and emesis.

2.5.3. PDE5

A large number of preclinical studies in rodents support the role of PDE5 inhibitors in cognition (Reneerkens et al., 2009). Most of these studies were performed with the PDE5 inhibitors sildanefil or zaprinast. More specifically, the results point to a beneficial role in episodic-like memory in unimpaired animals, as well as spatial working memory in impaired animals. Sildenafil also reversed the disruptive effect of a nitric oxide synthase inhibitor on spatial working memory (Devan et al., 2006). Some beneficial effects of sildenafil were also shown in Cynomolgus monkeys in an object retrieval task (Rutten et al., 2008).

With respect to clinical assessment, only studies with small numbers of subjects are available, with limited results. Some beneficial effect on reaction time in healthy volunteers was claimed (Grass et al., 2001) after acute treatment with sildenafil, but other studies in healthy volunteers only reported a limited increase on attention and no effect on memory (Schultheiss et al., 2001). A small clinical study in out-patients with schizophrenia stabilized on antipsychotics did not show a beneficial effect of adjunctive acute treatment with sildenafil on cognitive functions (Goff et al., 2009). Thus, contrary to the preclinical data set, the few clinical reports do not consistently support a strong role of PDE5 in attention, memory or performance of logic tasks in healthy volunteers or patients with schizophrenia.

2.5.4. PDE9

PDE9, a cGMP-specific PDE, is widely expressed in the brain, particularly in the cortex, hippocampus and striatum (Schmidt, 2010). With respect to preclinical data, the PDE9 inhibitor BAY 73-6691 improved memory consolidation in unimpaired rats and mice studied in object and social recognition tasks (van der Staay et al., 2008). Furthermore, this compound reversed MK-801- and scopolamine-induced memory deficits in the T-maze and in a passive avoidance task, respectively (van der Staay et al., 2008). With respect to clinical trials, Pfizer has conducted a Phase II study with PF-04447943 (see Table 1) in patients with mild to moderate AD (clinicaltrials.gov. Identificator NCT00930059); results are not yet public. In general, the impact of PDE9 on cognitive processing requires further investigation.

2.5.5. PDE10

PDE10, which affects both cAMP and cGMP, is highly expressed in striatal structures. It has been proposed that PDE10 inhibitors can treat the positive and negative symptoms as well as cognitive dysfunction in schizophrenia (Grauer et al., 2009; Zhang, 2010). MP10 (PF-0254920) from Pfizer is the furthest advanced PDE10 inhibitor. A Phase II study was initiated to evaluate whether MP10 is safe and effective for the treatment of schizophrenia (Table 1). With respect to preclinical research, several studies have been published on the nonspecific PDE10 inhibitor papaverine as well as the specific inhibitors TP10 (Reneerkens et al., 2009) and MP10 (Grauer et al., 2009). Fourteen days of treatment with papaverine induced impairment in spatial memory in mice when studied in the Morris water maze task (Hebb et al., 2008). Papaverine, after sub-chronic

treatment, also reversed PCP-induced impairment of executive function in rats (Rodefer et al., 2005). Contrary to the effects with papaverine, MP10 is inactive in rats when assessed for episodic-like memory in a novel object recognition paradigm (Grauer et al., 2009). However, these authors found papaverine and MP10 active in reversing MK-801 impaired social memory in mice. Together, the data suggest that specific PDE10 inhibitors have potential in treating cognitive dysfunction specific to certain cognitive domains, particularly social memory and executive function (Simson et al., 2010).

2.6. Dopaminergic targets

In the dopamine receptor family, D_1, D_3, and D_4 receptors have been targets for cognition enhancement. Perhaps the strongest case can be made for dopamine D_1 receptor agonists and D_1 receptor signaling within the prefrontal cortex (Goldman-Rakic et al., 2004). However, there is no active clinical development of D_1 receptor agonists at this time (Table 1). Pro-cognitive effects have been shown for dopamine D_3 receptor antagonists. In particular, the D_3 receptor antagonists S33084 and SB277,011 improved social recognition in rats (Loiseau and Millan, 2009). These effects seem to be linked to increased ACh activity in prefrontal structures (Panayi et al., 2005). Similarly, the D_2/D_3 receptor antagonist S33138 has pro-cognitive effects in tests for attention and working memory. S33138 also reversed the effect of scopolamine in social recognition (Millan et al., 2008). With respect to the dopamine D_4 receptor, preclinical data are limited. One compound, L745,870, a D_4 receptor antagonist, improved working and episodic memory (Braszko, 2010). Clinical data with dopamine modulators is forthcoming over the next few years, either with D_2 receptor stabilizer drugs or with D_3 receptor antagonists having mixed pharmacology.

2.7. Serotonergic targets

Malfunction of the 5-HT system has emerged as a leading candidate cause for depression (Middlemiss et al., 2002; Naughton et al., 2000). At the same time, several lines of evidence point to a role for 5-HT in memory (Buhot et al., 2000). Most prominently, depletion of tryptophan, a precursor of 5-HT, is associated with lower performance on episodic memory retention tests in humans (Riedel et al., 1999). This mirrors findings in depression which is accompanied by moderate to severe memory deficits (Johnson and Magaro, 1987; Schaub et al., 2003). However, manipulations that increase 5-HT concentration or 5-HT receptor activation also lower memory performance as indicated by receptor agonist studies in both humans (Riedel et al., 2002) and animals (Normile and Altman, 1988). Both increased and decreased 5-HT receptor activation have adverse effects on memory due to two actions of 5-HT in the hippocampus (Meeter et al., 2006). First, 5-HT exerts a hyperpolarizing influence on principal cells; directly, via 5-HT$_{1A}$ receptors, and indirectly, via facilitation of GABA release from local interneurons through 5-HT$_3$ receptors (Burnet et al., 1995; Piguet and Galvan, 1994). Activation of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors induce depolarization in principal cells (Barnes and Sharp, 1999; Piguet and Galvan, 1994), yet these effects appear to be dominated by the depolarizing effects of 5-HT as bath application of 5-HT will hyperpolarize principal cells in slice preparations of the dentate gyrus (Piguet and Galvan, 1994). In addition, through 5-HT$_{2C}$, 5-HT$_4$, and 5-HT$_7$ receptors, down-regulation of hyperpolarizing currents leads to reduced adaptation in principal cells (Bacon and Beck, 2000; Torres et al., 1996). The increased firing rate observed in slices after prolonged application of 5-HT has been linked to this mechanism (Andrade and Chaput, 1991; Andrade and Nicoll, 1987). In summary, 5-HT influences memory performance through its hyperpolarizing effects whereas changes in adaptation may not have a large influence on memory performance (Meeter et al., 2006). Distinct memory profiles can be derived for low and high transmission of 5-HT

in the hippocampus: low 5-HT transmission is predicted to lead to a relatively large amount of information being retrieved at the cost of activating irrelevant information and of high levels of false alarms. High 5-HT transmission was predicted to lead to a reduced quantity of retrieved information leading to lower recall scores combined with lower levels of false alarms.

To mediate the actions of 5-HT, at least 15 distinct 5-HT receptors have been identified which are divided into seven main families (5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$ and 5-HT$_7$); several families have many members (e.g., 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, and 5-HT$_{1F}$) (Roth et al., 2004). Each 5-HT receptor type or subtype has a specific regional distribution in the brain (Hoyer and Martin, 1996). In addition to the 5-HT transporter, which is widely distributed in the whole brain and mirrors 5-HT innervation, some specific 5-HT receptors, such as the 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_3$, 5-HT$_4$ and 5-HT$_6$ are potentially involved or have been implicated in memory function. One reason that 5-HT receptors are thought to be involved in cognition is implied by their neuroanatomical localization, especially in brain areas linked to memory such as the hippocampus, frontal cortex and striatum. 5-HT$_{1A}$ receptors are concentrated in the hippocampus, septum and raphe nucleus, as well as cortical regions, the latter of which is more richly populated by 5-HT$_{2A}$ receptors while 5-HT$_4$ receptors are abundant in basal ganglia and hippocampus. Others such as 5-HT$_3$ and 5-HT$_6$ receptors are abundant in cortical and hippocampal areas. Aside from this neuroanatomical distribution, the role of 5-HT receptors in learning and memory also depends on whether they are located on cholinergic septo-hippocampal and nucleus basalis of Meynert to frontal cortex pathways, or on the glutamatergic pyramidal cells present in the hippocampus, the subiculum, the entorhinal and the frontal cortices, or on the GABA-ergic interneurons in different regions, suggesting interactive influences between 5-HT and these different neurotransmission systems (Buhot et al., 2000).

2.7.1. 5-HT$_{1A}$ receptors

In the 1990s, several 5-HT$_{1A}$ agonists were studied for their effects on cognition; results were described with buspirone, flesinoxan, ipsapirone and umespirone (Friston et al., 1992; Grasby et al., 1992; Hart et al., 1991; Holland et al., 1994; Riedel et al., 2002; Unrug et al., 1997; Van Harten et al., 1996a,b) showing that 5-HT$_{1A}$ agonists have very modest cognition enhancing properties in normal elderly and in depressed patients. No significant development has resulted from these studies. Interestingly, 5-HT$_{1A}$ antagonists have also been targeted and were studied up to Phase III in AD patients, however, at present no 5-HT$_{1A}$ compounds are known to be in development (Patat et al., 2005; Pitsikas et al., 2005; Schechter et al., 2005). Several novel antipsychotics with 5-HT$_{1A}$ action such as lurasidone may have cognition-enhancing properties (Nakamura et al., 2009). Differences with existing antipsychotics have been shown to favor cognition enhancement in schizophrenia (Harvey et al., 2011), but there is no clinical evidence that this is specifically due to 5-HT$_{1A}$ action, or any other serotonergic action (e.g., 5-HT$_6$ or 5-HT$_7$). Although it is fair to say that the latter 5-HT mechanisms cannot be ruled out, the complete lack of anticholinergic and antihistaminergic properties provides a potentially much more parsimonious explanation for a relatively more cognition sparing effect of these drugs when compared to existing antipsychotics.

2.7.2. 5-HT$_{2A}$ receptors

In an earlier review (Roth et al., 2004) it was suggested that drugs with potent 5-HT$_{2A}$ antagonistic actions may prove beneficial at improving cognition in schizophrenia and dementia due to a close association between NMDA and 5-HT$_{2A}$ receptors. In line with this, the selective 5-HT$_{2A}$ antagonist, EMD 281014, improved working memory function in both young and aged monkeys (Terry et al., 2005). It was also demonstrated in humans and monkeys that 5-HT$_{2A}$ agonism impaired working memory (Umbricht et al., 2003; Williams et al.,

2002). However, at present no compounds aimed at 5-HT$_{2A}$ receptors are known to be in development solely for cognitive benefit.

2.7.3. 5-HT$_4$ receptors

In addition to providing symptomatic relief, 5-HT$_4$ receptor agonists have the potential to modify the pathogenesis of AD. In transfected Chinese hamster ovary cells and a human neuroblastoma cell line, 5-HT$_4$ receptor activation not only stimulated secretion of the soluble nonamyliodogenic form of the amyloid precursor protein (sAPP-alpha), which has neuroprotective, neurotrophic and cognitive enhancing effects, but also decreases extracellular accumulation of amyloid beta (King et al., 2008). Evidence suggesting that 5-HT$_4$ receptor polymorphisms could predispose individuals to schizophrenia (Suzuki et al., 2003) and ADHD (Li et al., 2006) is limited, whereas more interest has focused on neurodegenerative disorders such as AD, which is associated with decreased 5-HT$_4$ receptor expression in the hippocampus and prefrontal cortex (Reynolds et al., 1995). For example, PRX-03140 (Table 1), a highly selective, small-molecule 5-HT$_4$ receptor agonist, is currently being evaluated in Phase II clinical trials for the treatment of AD (clinicaltrials.gov; study identifiers ID NCT00384423, ID NCT00672945, and ID NCT00693004).

2.7.4. 5-HT$_6$ receptors

Recently, 5-HT$_6$ receptor antagonists with improved affinity and selectivity have been developed that demonstrate better penetration into the CNS (Russell and Dias, 2002). SB-742457 is a 5-HT$_6$ receptor antagonist in early clinical evaluation at GlaxoSmithKline for the treatment of AD (Table 1). A randomized, double-blind, placebo-controlled Phase II study investigated the efficacy and tolerability of SB-742457 in over 300 patients with mild-to-moderate probable AD; it was concluded that SB-742457 was generally safe and well tolerated and may be efficacious in AD (Maher-Edwards et al., 2010). Several other 5-HT$_6$ receptor antagonists are in development (Table 1) (Upton et al., 2008).

2.8. Histaminergic targets

The neurotransmitter histamine has long been implicated in cognitive functioning. Generally, studies in animals have shown a decline in performance after decreasing histamine neurotransmission and improved performance after increasing histamine neurotransmission. It is unclear, however, what role histamine plays in cognition in humans, which mainly stems from studies on the effects of H$_1$ receptor antagonists on cognitive performance. Also, the recent interest in H$_3$ receptors as a target has, in turn, stimulated human cognition research with histamine H$_1$ receptor antagonists (Turner et al., 2006; Van Ruitenbeek et al., 2009a,b, 2008, 2010a,b). An inventory of the literature furthermore confirmed that psychomotor skills and attention were most frequently impaired by lowering histamine; memory was the least impaired. Tasks assessing memory that were affected usually required rapid responses. It was concluded that both the complexity of the task as well as the demand for information processing speed determines the sensitivity to the effects of central H$_1$ receptor antagonism (Van Ruitenbeek et al., 2010c).

2.8.1. Histamine H$_1$ and H$_2$ receptors

The histaminergic cells in the tuberomammillary nucleus project to most areas of the brain where activation of postsynaptic H$_1$ and H$_2$ receptors leads to excitatory transmission or increased neuronal firing (Haas et al., 2008). Histaminergic transmission is terminated primarily by enzymatic breakdown and inhibition of synthesis and release via activation of presynaptic H$_3$ autoreceptors (Arrang et al., 1983). The role of histamine in sleep/wake regulation is well established (Monti, 1993; Saper et al., 2005). Next to its role in arousal, the widespread presence of histaminergic projections and receptors suggest a role in various CNS functions, including cognitive performance. Animal studies support an important role for histamine in cognitive functioning. A recent review of these studies (Alvarez, 2009) shows that reductions in histaminergic activity, due to lesions of the tuberomammillary nucleus or administration of H$_1$- and/or H$_2$-antagonists affect performance on tasks of learning and memory. Relatively little is known, however, about the specific role of histamine in human cognition, as compared to other monoamine neurotransmitters. In spite of the large number of studies that have been conducted assessing the effects of antihistamines or H$_1$ receptor antagonists on human performance, few attempts have been made to determine the cognitive domains most vulnerable to histaminergic dysfunction (Van Ruitenbeek et al., 2010a). It has been consistently shown, however, that H$_1$ receptor antagonists have no effect on episodic memory in humans but do impair working memory, attention, speed of processing, psychomotor processes and subjective arousal (Curran et al., 1998; Turner et al., 2006; Van Ruitenbeek et al., 2009a,b, 2008, 2010b,c).

2.8.2. Histamine H$_3$ receptors

Histamine H$_3$ receptor antagonists are currently under evaluation in clinical trials for a number of CNS illnesses including cognitive disorders in dementia, CIAS, narcolepsy and excessive daytime sleepiness. Blocking the H$_3$ receptor in animal brain leads to increased performance on many tasks assessing cognitive functioning (Esbenshade et al., 2008, 2006; Leurs et al., 1998; Vohora, 2004; Wijtmans et al., 2007; Witkin and Nelson, 2004). Performance on learning and memory tasks were notably improved in animals that otherwise show impaired performance. For example, mice that showed early signs of senescence improved their performance on tasks assessing memory consolidation after being treated with the H$_3$ antagonist thioperamide (Meguro et al., 1995). This drug was also able to reverse scopolamine induced spatial orientation, working memory and passive avoidance impairments in animals (Komater et al., 2005; Medhurst et al., 2007). In addition, H$_3$ receptor antagonists attenuated deficits in animal models for impairments seen in schizophrenia to the same degree as antipsychotic drugs (Akhtar et al., 2006; Browman et al., 2004; Fox et al., 2005). These and other data support the notion that H$_3$ receptor antagonists may be effective drugs for cognitive disturbances in humans. Further to this, a number of H$_3$ receptor antagonists are in clinical development for AD and CIAS (Table 1).

3. Perspectives

It is clear that the investment in research by academia, government and industry in the area of cognition is vast. The basic research that is leading to a better understanding of learning and memory itself is quite extensive, and it is through this that drug development for disorders of cognition will advance. It is difficult to predict which drug targets will be most beneficial to patients. In the area of symptomatic treatment for AD, a number of drug classes could come forward and replace or augment AChEIs. Some are well into clinical development and may compensate for the early cognitive deficits in patients with AD or related disorders associated with memory decline in aging populations (e.g., nicotinic agonists). Since the introduction in 2002 of the National Institute of Mental Health-sponsored initiative called Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) with collaborators from many research sectors (Green et al., 2004), a number of experimental compounds have entered clinical trial. To date, though, none has met with much success perhaps because of lack of efficacy, tolerability, clinical trial design or sensitivity of the test battery. The latter point is important to bear in mind when testing the efficacy of novel compounds in preclinical behavioral paradigms; for example, co-administration of a new drug with existing medications for a disorder may markedly modify its therapeutic effect and, thus, this should be studied prior to clinical testing. Nonetheless, like for AD, there remains a remarkable

push to assess the effectiveness of drugs representing different pharmacological targets for the treatment of CIAS. Of course, there is cognitive impairment across a wide number of other neuropsychiatric indications, ranging from Parkinson's and ADHD to neurodevelopmental disorders such as Down syndrome or FXS (Fig. 1). As the detrimental effects on attention, learning, memory and executive processes differ across the various disorders, it is probable that future effective drugs will be directed towards a different molecular mechanism in each disorder.

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