Translating the *N*-methyl-D-aspartate receptor antagonist model of schizophrenia to treatments for cognitive impairment in schizophrenia

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Abstract

The *N*-methyl-D-aspartate receptor (NMDAR) antagonists, phencyclidine (PCP), dizocilpine (MK-801), or ketamine, given subchronically (sc) to rodents and primates, produce prolonged deficits in cognitive function, including novel object recognition (NOR), an analog of human declarative memory, one of the cognitive domains impaired in schizophrenia. Atypical antipsychotic drugs (AAPDs) have been reported to improve declarative memory in some patients with schizophrenia, as well as to ameliorate and prevent the NOR deficit in rodents following scNMDAR antagonist treatment. While the efficacy of AAPDs to improve cognitive impairment in schizophrenia (CIS) is limited, at best, and controversial, single doses of all currently available AAPDs so far tested transiently restore NOR in rodents following scNMDAR antagonist treatment. Typical antipsychotic drugs (APDs), e.g. haloperidol and perphenazine, are ineffective in this rodent model, and may be less effective as treatments of some domains of CIS. Serotonergic mechanisms, including, but not limited to serotonin (5-HT)$_{2A}$ and 5-HT$_7$ antagonism, 5-HT$_{1A}$, and GABA(A) agonism, contribute to the efficacy of the AAPDs in the scNMDAR antagonist rodent models, which are relevant to the loss of GABA interneuron/hyperglutamate hypothesis of the etiology of CIS. The ability of sub-effective doses of the atypical APDs to ameliorate NOR in the scNMDAR-treated rodents can be restored by the addition of a sub-effective dose of the 5-HT$_{1A}$ partial agonist, tandospirone, or the 5-HT$_7$ antagonist, SB269970. The mGluR2/3 agonist, LY379268, which itself is unable to restore NOR in the scNMDAR-treated rodents, can also restore NOR when given with lurasidone, an AAPD. Enhancing cortical and hippocampal dopamine and acetylcholine efflux, or both, may contribute to the restoration of NOR by the atypical APDs. Importantly, co-administration of lurasidone, tandospirone, or SB269970, with PCP, to rodents, at doses 5–10 fold greater than those acutely effective to restore NOR following scNMDAR treatment, prevents the effect of scPCP to produce an enduring deficit in NOR. This difference in dosage may be relevant to utilizing AAPDs to prevent the onset of CIS in individuals at high risk for developing schizophrenia. The scNMDAR paradigm may be useful for identifying possible means to treat and prevent CIS.

Introduction

Improving cognitive impairment in schizophrenia (CIS) is critically important for improving functional outcome in schizophrenia. An understanding of the main features of CIS is essential to develop therapies which can prevent or treat CIS. CIS is the product of neurodevelopmental abnormalities, based upon genetic predispositions and experiential factors, which may affect gene expression (Faludi and Mirnics, 2011). CIS begins in early childhood

and adolescence, increases markedly during the prodromal period of schizophrenia, and worsens after the onset of psychosis (Saykin et al., 1991; Kremen et al., 1994; Waddington et al., 1998; Niendam et al., 2006; Kalkstein et al., 2010), and is a major contributor to poor functional outcome in schizophrenia (Green et al., 2004). Which cognitive domains are most affected and contribute the most to poor outcome varies among patients (Kenny and Meltzer, 1991; Saykin et al., 1991; Meltzer and McGurk, 1999). It has been suggested that there is a generalized cognitive factor which underlies CIS (Dickinson et al., 2004). However, efforts to develop treatments for a general cognitive factor underlying CIS have usually been unsuccessful and would seem difficult to reconcile with the marked variation in types and severity of cognitive deficits seen in schizophrenia. Thus, a variety

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of mechanisms might be suspected as being responsible for different components of CIS, requiring different pharmacologic treatments. Indeed, some treatments for some domains of cognition may impair other domains, e.g. over stimulation of dopamine (DA) D_1 receptors (Horiguchi et al., 2011a).

It has been concluded, based mainly on the cognitive data from the influential US-based CATIE clinical trial (Keefe et al., 2007), that the typical and atypical APDs (TAPDs, AAPDs), as well as a variety of drugs which have been tested as augmenting agents to improve CIS, e.g. glycine, D-serine, cholinesterase inhibitors, etc, produce inconsequential effects for CIS (Buchanan et al., 2007; Ibrahim and Tamminga, 2012; see Keefe and Harvey, 2012 for review). This conclusion rejects the evidence that both TAPDS and AAPDs produce clinically significant cognitive benefits in some domains of cognition, especially semantic memory, declarative memory and speed of processing, in 25–50% of schizophrenia patients, while improvements in working memory and executive function deficits are less common, but do occur (Meltzer and McGurk, 1999; Harvey and Keefe, 2001; Bilder et al., 2002; Wagner et al., 2005; Woodward et al., 2005). The extent of this improvement is greater for AAPDs than TAPDS. Appreciation of the variable but still significant benefits for some types of cognition focuses the effort on finding treatments *that may be* effective for only one or a few of the cognitive domains, particularly those only rarely improved by AAPDs. In addition, the use of AAPDs is favoured over TAPDs because of their more limited ability to cause motor side effects and prolactin elevations (Meltzer, 2013). It is accepted that TAPDs and AAPDs do not differ in overall efficacy for treating positive symptoms in non-treatment resistant schizophrenia patients. However, as with cognition, individual patients may respond better to specific antipsychotic drugs (Ramsey et al., 2011).

Were treatment with the AAPDs to produce no improvement in CIS, then any of the effects of AAPDs on neurotransmitters, neuromodulators, cortical and hippocampal function, which influence cognitive function, in rodents and primates, which have been demonstrated after AAPD treatment (see Meltzer and Huang, 2008; López-Gil et al., 2010; Yuen et al., 2012; Gacsályi et al., 2013), would have to be rejected as targets for developing novel drugs for CIS. This includes enhancing cortical and hippocampal DA, acetylcholine, (ACh), glutamate (Glu) and serotonin (5-HT) efflux, enhancing cortical gamma rhythms and increasing glutamate receptor currents, to name the most important candidates for improving cognition which have been reported to result from AAPD and not TAPD treatment (Meltzer and Huang, 2008; Yuen et al., 2012).

This review will emphasize the effects of subchronic (sc) administration of NMDAR non-competitive or uncompetitive antagonists, particularly PCP, ketamine, and MK-801, to produce enduring deficits in declarative memory in rodents. Similar deficits have been noted in primates (Elsworth et al., 2012). The acute deficits brought about by single doses of NMDAR antagonists have been recently reviewed by Gilmour et al. (2012), who concluded that this manner of utilizing NMDAR antagonists to model CIS did not correspond well with clinical data and differed from one NMDAR antagonist to another. The scNMDAR rodent model has been extensively utilized to develop treatments for CIS (Nabeshima et al., 2006; Meltzer et al., 2011; Gilmour et al., 2012) and, as will be discussed, shows a striking advantage for AAPDs over TAPDs. Interestingly, studies in transgenic mouse models (e.g. dominant negative C-terminal truncated DISC1) also show greater efficacy of AAPDs compared to TAPDs to ameliorate the deficit in NOR (Nagai et al., 2011).

The scNMDAR antagonist model of cognitive impairment in schizophrenia

Novel object recognition (NOR) in rodents has received extensive study as a model of the deficits in declarative memory in schizophrenia and other neuropsychiatric disorders (Neill et al., 2010; Meltzer et al., 2011; Lyon et al., 2012). Declarative memory in rodents is markedly impaired by sc treatment with each of the three most frequently studied NMDAR antagonists, PCP, MK-801 and ketamine (Ennaceur and Delacour, 1988; Nabeshima et al., 2006; Karasawa et al., 2008; Young et al., 2009; Snigdha et al., 2010; Horiguchi et al., 2011a,b,c; see Neill et al., 2010; Meltzer et al., 2011 for review). Deficits in executive function and working memory have also been shown to result from 7–10 d consecutive treatment with an NMDAR antagonist (Neill et al., 2010; Bado et al., 2011; Li et al., 2011). The doses of PCP, ketamine and MK-801 needed to establish these deficits are in the same range as those that increase locomotor activity, a surrogate for their psychotomimetic effects (Meltzer et al., 2011). However, they are lower than the doses which produce neurodegeneration (Kim et al., 1999).

Supporting the validity of the NMDAR antagonist model of CIS, acute administration of the NMDAR non-competitive antagonist, ketamine, impairs some domains of cognition and provokes psychotic symptoms in both normal subjects and patients with schizophrenia. Clozapine, the prototypical AAPD, diminished ketamine-induced cognitive impairment in patients with schizophrenia (see Kantrowitz and Javitt, 2010 for review). Newcomer et al. (1999) reported that an intravenous infusion of ketamine at sub-anesthetic doses, to male normal volunteers, produced deficits in declarative memory without impairing selective or sustained attention or verbal fluency.

Declarative memory and NOR

Almost all patients with schizophrenia perform 1–2 S.D. below normal on declarative memory tasks (Saykin

et al., 1991). They also show deficits in two-dimensional object recognition tasks (Heckers et al., 2000; Sehatpour et al., 2010). Recognition memory, as well as long term verbal memory, is known to involve the hippocampus, the retrosplenial and perirhinal cortex and the prefrontal cortex (PFC) (Ullman, 2001). High doses of PCP have been shown to produce maximal neurodegeneration in the retrosplenial cortex (Kim et al., 1999), but the doses used in CIS studies spare the retrosplenial cortex (Rajagapol and Meltzerl, in preparation). It is likely that the relatively low dose scNMDAR treatment used in CIS studies in rodents produce functional disruption only, since a variety of acute treatments readily reverse the scNMDAR antagonist deficits in cognition in both rats and mice (Neill et al., 2010; Meltzer et al., 2011; Rajagopal and Meltzer, in preparation), similar to their ability to block the effects of acute doses of NMDAR antagonists on cognition (Neill et al., 2010; Meltzer et al., 2011). Thus, it is possible that the failure of the AAPDs to improve CIS in some patients with schizophrenia is due to more irreversible structural damage.

The NOR paradigm utilized in our rodent studies has been described in detail elsewhere (Hashimoto et al., 2005; Horiguchi et al., 2011a). Normal rodents explore novel objects for greater periods of time than familiar objects, which is the basis for calculation of a discrimination index (DI). The DI is the difference between the time spent exploring the novel object and the time spent exploring the familiar object, divided by the total exploration time.

Atypical antipsychotic drugs acutely reverse NOR deficits induced by scNMDAR antagonists: the role of 5-HT

The deficits in NOR produced by administration of sc PCP, MK-801, or ketamine, for 7 d produces deficits in NOR in mice and rats lasting for weeks to months, if not indefinitely, which indicates the drug treatment resets circuitry in a potentially permanent manner, which nevertheless is reversible (see Nabeshima et al., 2006: Neill et al., 2010; Meltzer et al., 2011 for reviews). Remarkably, all AAPDs studied to date, including single doses of amisulpride, aripiprazole, asenapine, blonanersin, clozapine, N-desmethylclozapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone and ziprasidone, administered systemically, have been found to be effective to restore NOR in mice or rats, when given shortly before the acquistion phase, i.e. exposure to two identical objects (Nagai et al., 2009; Neill et al., 2010; Meltzer et al., 2011, Rajagopal and Meltzer, in preparation). The effective doses of the AAPDs do not interfere with locomotor activity and are comparable to the doses which block PCP-induced locomotor activity (Meltzer et al., 2011), suggesting that they are clinically relevant. As shown in Fig. 1, sc PCP treatment for 7 d followed by withdrawal for 7 d during which the rodents
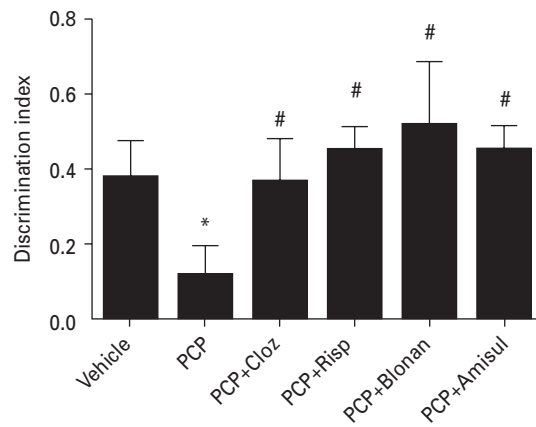
Fig. 1. The effect of sub-chronic (sc) vehicle(0.9% saline), sc PCP (2 mg/kg; i.p.) given twice a day for 7 d followed by a 7 d drug-free period (as previously described in Horiguchi et al., 2011a); acute clozapine (0.3 mg/kg), risperidone (0.1 mg/kg), blonanserin (1 mg/kg), and amisulpride (10 mg/kg) on the discrimination index (DI) in female Long–Evans rats. Data are expressed as mean±S.E.M. (N=7–9 per group). *p<0.05; significant reduction in DI when compared to vehicle animals. #p<0.05; significant increase in DI when compared to the PCP treated animals.

are habituated to the NOR chamber significantly impaired NOR in Long–Evans female rats. Pretreatment with the AAPDs clozapine (0.3 mg/kg), risperidone (0.1 mg/kg), blonanserin (1.0 mg/kg), and amisulpride (10 mg/kg) restored NOR. To our knowledge, there are no studies which report that TAPDs ameliorate the deficit in rodent NOR produced by sc treatment with NMDAR antagonists (Grayson et al., 2007; Karasawa et al., 2008; McLean et al., 2009a,b; Nagai et al., 2009; Snigdha et al., 2010; Idris et al., 2010; Jenkins et al., 2010; Horiguchi et al., 2011a,b,c; Rajagopal and Meltzer, in preparation; see Meltzer et al., 2011 for review). By contrast, the efficacy of both AAPDs and TAPDs to improve any domain of cognition in schizophrenia, including declarative memory, is controversial (Harvey and Keefe, 2001; Woodward et al., 2005; González-Blanch et al., 2008). Measurement issues and enduring effects of prior treatment may account for some of the conflicting results (Stone and Hsi, 2011). What appears to be indisputable is that the AAPDs substantially improve some domains of cognition, including declarative memory, in *some* patients with schizophrenia (Hagger et al., 1993; see Woodward et al., 2005 for review), a syndrome whose heterogeneity in etiology, course and response to treatment of positive and negative symptoms is well established (Meltzer, 2013).

Role of 5-HT$_{2A}$ receptors in scNMDAR-antagonist induced deficits in NOR

It has been clearly established that serotonergic mechanisms play a central role in learning and memory

(Meneses, 1999; Buhot et al., 2000; Codony et al., 2011), as well as psychosis and motor function (Meltzer and Huang, 2008). AAPDs achieve many of their effects via actions on multiple 5-HT receptors, not just via 5-HT$_{2A}$ receptor antagonism relative to D$_2$ receptor antagonism (Meltzer and Huang, 2008). These include actions at 5-HT$_{1A}$, 5-HT$_{2C}$, 5-HT$_6$, and 5-HT$_7$ receptors (Meltzer and Huang, 2008). Asenapine and clozapine are the only AAPDs which act at all of these 5-HT receptors at doses that are clinically relevant (Meltzer and Huang, 2008; Shahid et al., 2009). The overall efficacy and side effect profile of each AAPD is influenced by its effects on those 5-HT receptors which they directly, or as is the case with the 5-HT$_{1A}$ receptor for some AAPDs, indirectly modulate (Meltzer and Huang, 2008). All of the above listed 5-HT receptors have been shown to participate in specific aspects of cognitive function, but others may as well, especially the 5-HT$_3$ and 5-HT$_4$ receptor (Meneses, 2007). These receptors are important for the deficit in NOR in rodents produced by sc treatment with NMDAR antagonists, and the treatments which can reverse, or even prevent, the effects of the NMDAR antagonists to produce the deficit (Meltzer et al., 2012b).

We have recently utilized a new mass spectroscopic–liquid chromatographic method to measure multiple neurotransmitters in the same sample obtained by microdialysis in freely moving rats or mice (Song et al., 2011). As shown in Fig. 2, an acute dose of PCP, 5 mg/kg, increased extracellular levels of 5-HT in rat mPFC and nucleus accumbens. Ketamine, 30 mg/kg, also enhanced efflux of 5-HT in the mPFC and hippocampus (Fig. 3; Huang and Meltzer, in preparation). It is unclear if repeated release of 5-HT during the development of the NOR deficit contributes to the emergence of CIS. Concomitant administration of a selective 5-HT$_{2A}$ inverse agonist, e.g. M100907, with PCP will not prevent the development of the NOR deficit in Long–Evans rats or C57Bl mice given sc PCP (Horiguchi et al., Rajagapol et al., unpublished data). The basis for this increase in extracellular 5-HT levels by NMDAR antagonists may be activation of dorsal and medial raphe 5-HT neurons as well as inhibition of the reuptake of 5-HT by a direct effect on the 5-HT transporter (Smith et al., 1977; Hori et al., 2000). Nabeshima et al. (1988) have reported that PCP, *in vitro*, like the 5-HT$_{2A/2C}$ inverse agonist, ritanserin, protected 5-HT$_{2A/2C}$ receptors from inactivation by sulfhydryl-modifying-agent, N-ethylmaleimide, suggesting that PCP due to its ability to enhance the extracellular concentrations of 5-HT as shown in Fig. 2. Sub-chronic treatment with PCP increased 5-HT$_{1A}$ receptor binding in the medial–prefrontal and dorsolateral–frontal cortex but had no effect on the density of cortical 5-HT$_{2A}$ receptors (Choi et al., 2009). However, Steward et al. (2004) reported that sc PCP treatment decreased 5-HT$_{2A}$ receptor binding, but not 5-HT$_{2A}$ mRNA, in the PFC, consistent with previous

reports for post-mortem brain tissue from schizophrenic patients.

The 5-HT$_{2A}$ receptor is the most abundant 5-HT receptor subtype in the cortex (Jones et al., 2009) and has been shown to play a key role in the transport and dynamic regulation of NMDARs in cortical pyramidal neurons (Yuen et al., 2005). 5-HT$_{2A}$ antagonism, which would be expected to block the firing of pyramidal neurons, and 5-HT$_{1A}$ receptor stimulation, produce comparable effects on the excitability of pyramidal neurons (Yuen et al., 2008). These authors demonstrated that activation of 5-HT$_{2A/2C}$ receptors significantly attenuated the effect of 5-HT$_{1A}$ receptor stimulation on NMDAR currents, microtubule depolymerization in PFC pyramidal neurons from intact animals treated with serotonergic drugs, as well as the inhibitory effect of 5-HT$_{1A}$ receptor stimulation on surface NR2B clusters of NMDAR on dendrites. This may be the basis for the ability of the 5-HT$_{2A}$ antagonist M100907 to promote long term potentiation (Arvanov and Wang, 1998).

We have reported that a higher ratio of affinities of AAPDs for 5-HT$_{2A}$ than D$_2$ receptors distinguishes AAPDs from TAPDs (Meltzer et al., 1989). The importance of limited D$_2$ receptor blockade to the action of the AAPDs to improve NOR is shown by the ability of small doses of haloperidol to prevent the effect of risperidone, which itself has high affinity for the D$_2$ receptor, to restore NOR in scPCP-treated rats (Snigdha et al., 2010). Blonanserin, an AAPD, is a highly selective antagonist of 5-HT$_{2A}$ and D$_2$ receptors (Oka et al., 1993). The effect of blonanserin is, nevertheless, blocked by WAY100635, a selective 5-HT$_{1A}$ antagonist (Horiguchi et al., in press). The ability of 5-HT$_{2A}$ antagonists such as M100907, ACP-103 (pimavanserin), and MDL 11939 to augment the efficacy of sub-effective doses of AAPDs (Snigdha et al., 2010; Rajagopal and Meltzer, in preparation), also supports the hypothesis that 5-HT$_{2A}$ and D$_2$ receptor antagonism is an important basis for the activity of the AAPDs to restore NOR in the scNMDAR antagonist model. As shown in Fig. 4, the 5-HT$_{2A}$ inverse agonist, pimavanserin, 3.0 mg/kg, the 5-HT$_{1A}$ partial agonist, tandospirone, 0.2 mg/kg and the 5-HT$_7$ antagonist, SB269970, 0.6 mg/kg, also restored the ability of a sub-effective dose of lurasidone, 0.03 mg/kg, to acutely reverse the effect of sc PCP administration in rats (Horiguchi et al., 2011b; Meltzer et al., 2011; Snigdha et al., 2011). This is consistent with our previous studies using microdialysis, which demonstrated that excessive D$_2$ receptor blockade can impair the ability of AAPDs to increase DA release in the rat. 5-HT$_{2A}$ receptor inverse agonists M100907 and pimavanserin do not by themselves acutely reverse the effects of sc PCP to disrupt rat NOR (Snigdha et al., 2010). Pimavanserin has been shown to potentiate the ability of a sub-effective dose of risperidone to improve psychopathology in acutely psychotic schizophrenia patients (Meltzer et al., 2012a). It did not enhance the efficacy of haloperidol 2 mg/d
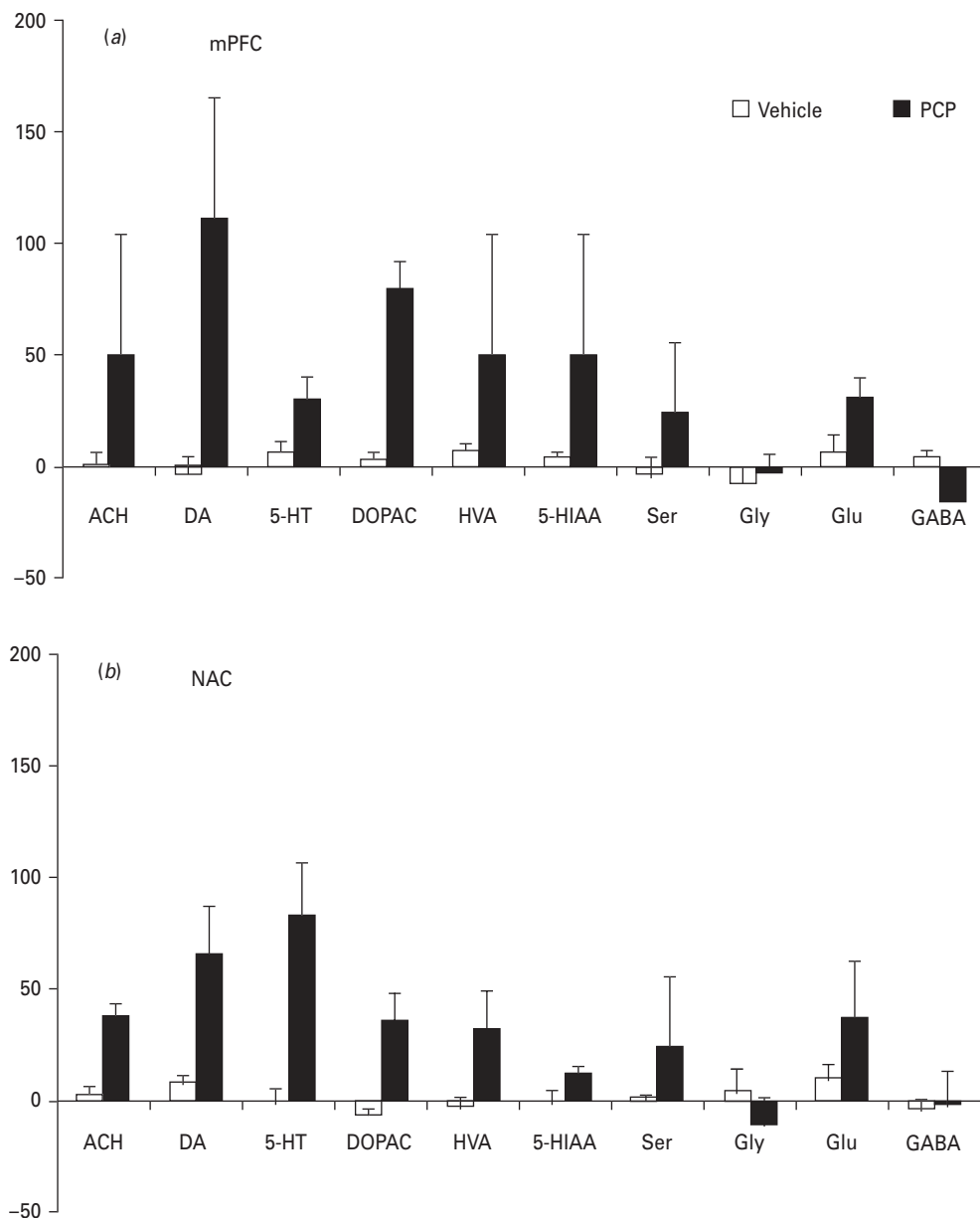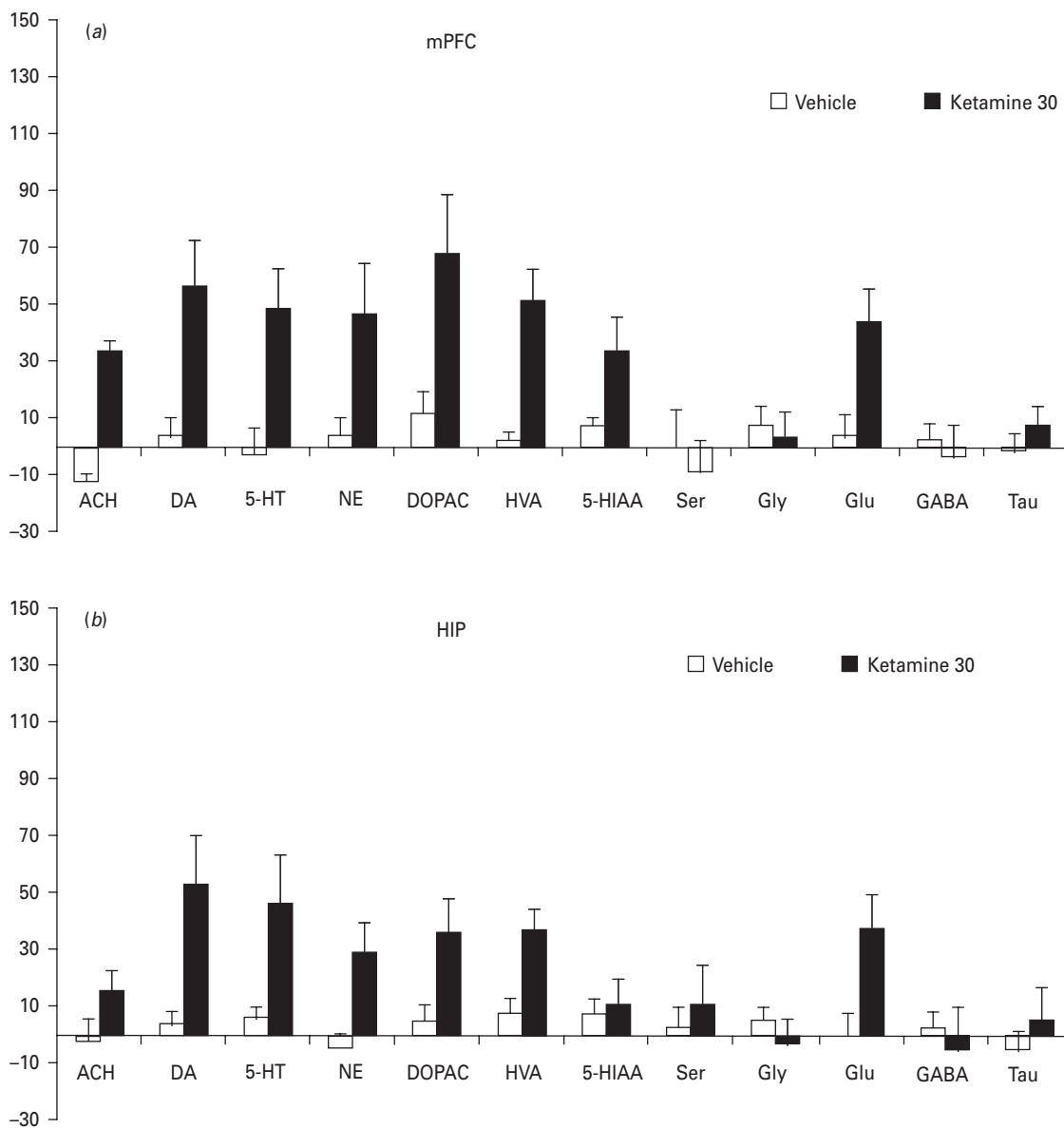
Fig. 2. The effect of PCP (5 mg/kg, i.p.) administered following a baseline sample collection (for 2 h) (as previously described in Huang et al. (2008)) on neurotransmitter efflux in rat mPFC (*a*) and NAC (*b*) reported as net area under the curve (AUC). ACH: acetylcholine; DA: dopamine; 5-HT: serotonin; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; 5-HIAA: 5-hydroxyindole acetic acid, Ser: serine; Gly: glycine; Glu: glutamate; and GABA: gamma-aminobutyric acid, (Huang and Meltzer, in preparation).

which was as effective as a full dose of risperidone. No measures of cognition were obtained in this study, however, so it remains to be determined if more extensive blockade of 5-HT$_{2A}$ receptors will enhance cognition in schizophrenia patients. In summary, 5-HT$_{2A}$ receptor blockade is a key component of the ability of atypical APDs such as clozapine which are more potent 5-HT$_{2A}$ than D$_2$ antagonists to reverse the effect of scNMDAR antagonists on cognition, but it is not effective on its own to prevent or ameliorate the impairment of memory induced by the NMDAR antagonists.

## Role of 5-HT$_{1A}$ receptor in NMDAR antagonist-induced deficits in NOR in rodents

Many AAPDs are themselves 5-HT$_{1A}$ partial agonists or are indirect 5-HT$_{1A}$ agonists, as indicated by the blockade of their central actions by WAY100635, a selective 5-HT$_{1A}$ antagonist (Meltzer and Huang, 2008). The 5-HT$_{1A}$ partial agonist, tandospirone (Tanaka et al., 1995; Newman-Tancredi et al., 1998), improved declarative memory in patients with schizophrenia taking TAPDs (Sumiyoshi et al., 2000, 2001a,b). There is considerable

Fig. 3. The effect of ketamine (30 mg/kg, i.p.) administered following a baseline sample collection (for 2 h) (as previously described in Huang et al., (2008)) on neurotransmitter efflux in mouse mPFC(A) and HIP(B) reported as net area under the curve (AUC). ACH: acetylcholine; DA: dopamine; 5-HT: serotonin; NE norepinephrin; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; 5-HIAA: 5-hydroxyindole acetic acid, Ser: serine; Gly: glycine; Glu: glutamate; GABA: gamma-aminobutyric acid, Tau: taurine (Huang and Meltzer, in preparation).

evidence that 5-HT$_{1A}$ receptor stimulation by itself, and as augmentation of AAPDs, also enhances NOR in PCP-treated rats (Horiguchi et al., 2012) as well as social deficits (Snigdha and Neill, 2008) and impaired reversal learning (McLean et al., 2009a,b). 5-HT$_{1A}$ partial agonism contributes to the ability of the atypical AAPD aripiprazole to restore NOR and social interaction in aripiprazole-treated rodents (Snigdha and Neill, 2008; Nagai et al., 2009). Also, tandospirone and F15599, a selective post-synaptic 5-HT$_{1A}$ agonist, restored NOR in PCP-treated rats (Horiguchi and Meltzer, 2012), possibly by inhibiting fast spiking GABA interneurons, leading to enhanced activity of pyramidal neurons (Lladó-Pelfort et al., 2012). Tandospirone had a similar effect in C57Bl/6J mice (Rajagopal and Meltzer, in preparation). The combination of sub-effective doses of tandospirone (0.2 mg/kg) and lurasidone (0.03 mg/kg) also reversed the PCP-induced NOR-deficit (Horiguchi and Meltzer, 2012). WAY100635, a selective 5-HT$_{1A}$ antagonist, also blocked the ameliorating effects of tandospirone and lurasidone, but not amisulpride, in sc PCP-treated rats (Horiguchi and Meltzer, 2012; Horiguchi et al., unpublished data). Interestingly, haloperidol, 0.1 mg/kg, prevents tandospirone from attenuating the effect of sc PCP
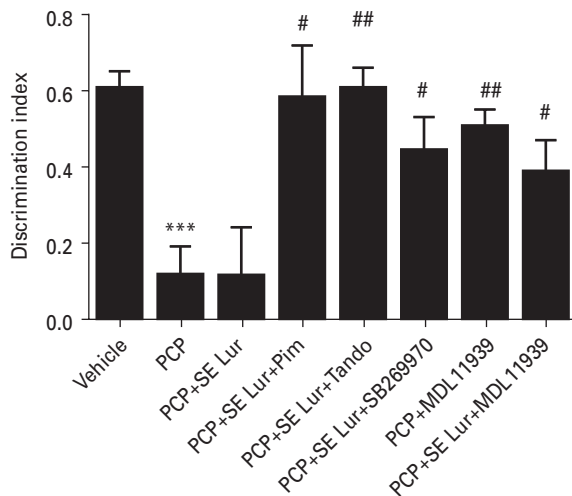
Fig. 4. The effect of sc vehicle (0.9% saline), sc PCP (2 mg/kg; i.p.) given twice a day for 7 d followed by a 7 d drug-free period (as previously described in Horiguchi et al., 2011a); acute sub-effective(s.e.) lurasidone (0.03 mg/kg), s.e. lurasidone+s.e. pimavanserin (3 mg/kg); s.e. lurasidone+s.e. tandospirone (0.2 mg/kg), and s.e. lurasidone+SB269970 (0.1 mg/kg), on the DI in female Long–Evans rats. Data are expressed as mean±s.e.m. (N=7–9 per group). ***$p < 0.001$; significant reduction in DI when compared to vehicle animals. #$p < 0.05$; ##$p < 0.01$; significant increase in DI when compared to the PCP treated animals.

treatment (Horiguchi and Meltzer, 2012), as well as risperidone and lurasidone (Snigdha et al., 2010; Horiguchi and Meltzer, 2012).

Stimulation of 5-HT$_{1A}$ receptors may also prevent the development of the NMDAR-antagonist induced deficit in cognition. WAY100635 (1.0 mg/kg) blocked the ability of sc treatment (14 d) with the AAPD, perospirone (1.0, 3.0, or 10 mg/kg), to attenuate subchronic PCP (10 mg/kg)-induced cognitive deficits in mice (Hagiwara et al., 2008). We have found that lurasidone (1.0 mg/kg), or tandospirone, 5.0 mg/kg, but not lower doses of these drugs which ameliorate the PCP-induced deficit in NOR, nor pimavanserin or haloperidol, significantly prevented the PCP-induced NOR deficit. The preventive effect of lurasidone was blocked by WAY100635, indicating the protective effects was based upon its 5-HT$_{1A}$ partial agonism (Horiguchi et al., 2012).

As previously mentioned, sc treatment with PCP increases 5-HT$_{1A}$ receptor binding in the medial–prefrontal and dorsolateral–frontal cortex (Choi et al., 2009). An increase in 5-HT$_{1A}$ receptor density has been reported in post-mortem tissue from the frontal and temporal cortices of schizophrenia patients (Hashimoto et al., 1991; Burnet et al., 1996, 1997; Sumiyoshi et al., 1996). The upregulation of 5-HT$_{1A}$ receptors may be a compensatory mechanism to stabilize pyramidal neurons which are hyperpolarized by 5-HT$_{1A}$ receptor stimulation (Andrade and Nicoll, 1987). Increased inhibitory influence on pyramidal neurons would be beneficial after sc PCP administration because of the loss of GABAergic

interneurons (Abdul-Monim et al., 2007; Thomsen et al., 2009) which regulate the firing of pyramidal neurons in the hippocampus and cortex. This loss of parvalbumin-containing GABA neurons parallels the decrease in GABAergic interneurons in the brains of patients with schizophrenia (Bennett, 2011). The α7 nicotinic ACh receptor partial agonist, SSR180711 dose-dependently reversed the deficit in a modified Y-maze test in mice treated with PCP 10 mg/kg for 10 d followed by a wash-out. Co-administration of SSR 180711 with PCP prevented the decrease in parvalbumin-containing GABA neurons noted above, further supporting the relevance of the PCP model of CIS (Thomsen et al., 2009). Taken together, these results suggest 5-HT$_{1A}$ partial agonism is important to the ability of AAPDs to prevent or ameliorate the NMDAR-antagonist model of CIS.

Role of 5-HT$_7$ receptor in NMDAR antagonist-induced deficits

The 5-HT$_7$ receptor is a G-protein coupled receptor positively coupled to adenylate cyclase. It is expressed in brain regions, including the thalamus, limbic regions, hippocampal formation, and frontal cortex, that are involved in psychosis, learning and memory (To et al., 1995; Hedlund, 2009; Roberts and Hedlund, 2012). Some TAPDs and AAPDs, including amisulpride, clozapine, lurasidone and risperidone, have low nano-molar affinity for the 5-HT$_7$ receptor (Roth et al., 1994; Horiguchi et al., 2011b). 5-HT$_7$ receptor mRNA expression levels are significantly decreased in brain tissue from schizophrenia patients (Dean et al., 2006). Evidence for both a procognitive and memory impairing role for 5-HT$_7$ receptors has been obtained from studies using 5-HT$_7$ knock out mice and specific 5-HT$_7$ antagonists in rodents. There is evidence that blockade of 5-HT$_7$ receptors may have a procognitive effect in rodents subchronically treated with NMDA receptor antagonists. The ability of amisulpride and lurasidone to ameliorate the deficit in NOR produced by sc PCP administration is blocked by the 5-HT$_7$ agonist, AS19 (Horiguchi et al., 2011b). SB269970 also potentiated sub-effective doses of lurasidone and amisulpride, but not haloperidol, to restore NOR in PCP-treated rats (Horiguchi et al., 2011b; Oyamada et al., in preparation). We have also found that SB269970, 1 mg/kg, acutely reversed PCP- and MK-801-induced NOR deficits in C57/BL male mice (Rajagopal and Meltzer, in preparation). Mice lacking pituitary adenlate cyclase-activating polypeptide (PACAP), a transgenic mouse model of relevance to schizophrenia and depression, have deficits in working memory in the spontaneous alternation in the Y-maze task. SB 269970, 1 mg/kg, reversed this deficit (Tajiri et al., 2012). The beneficial effects of SB 269970 on cognition might be the result of enhanced release of GABA (Tokarski et al., 2011). In agreement with this suggestion, SB269970, 3.0 mg.kg, significantly increased cortical DA,

glutamate, and GABA efflux in C57BL/6J mice (Huang and Meltzer, in preparation).

Prenatal, perinatal and adolescent administration of NMDAR antagonists as models of CIS

Schizophrenia as a syndrome, and CIS in particular, have been considered to be due, in part, to abnormalities in neurodevelopment (Faludi and Mirnics, 2011). This does not exclude neurodegenerative processes exacerbating CIS at any stage of its evolution, especially during periods of stress (Piper et al., 2012). PCP, MK-801 and ketamine have been administered during gestational, neonatal, perinatal and juvenile periods to induce cognitive impairment later in development (Schwabe et al., 2006; Dong et al., 2012; see Powell, 2010 for review). Such studies can contribute to knowledge about the role of hypoglutamatergic function in the development of CIS and to determining whether such models can be helpful to develop treatments that might prevent the development of CIS (Beneyto and Lewis, 2011). Nakatani-Pawlak et al. (2009) reported that the impairment of social interaction behaviour following neonatal PCP was significantly reversed by administration of clozapine. Neonatal administration of PCP or MK-801 in rodents has been reported to decrease parvalbumin-positive cells and spine density, (Wang and Johnson, 2005; Nakatani-Pawlak et al., 2009), both of which have been reported in schizophrenia (Beneyto and Lewis, 2011). Neonatal NMDAR antagonists have been shown to cause deficits in attentional set shifting (Broberg et al., 2008), novelty discrimination (Terranova et al., 2005; Harich et al., 2007; Pichat et al., 2007; Boulay et al., 2008), reversal and spatial working memory tasks in the Morris water maze, and in the delayed-non-match-to-position task (Kawabe and Miyamoto, 2008). There is a need for identification of drugs and other treatments which prevent the effects of NMDAR on neurodevelopment and which might be tolerable for individuals at high risk for schizophrenia who might be willing to test neuroprotective treatments.

There is no evidence, as of yet, that AAPDs are effective in preventing the development of cognitive impairment when administered to individuals thought to be at high risk for developing schizophrenia (Fleischhacker and Simma, 2012). This may be because drugs, including AAPDs, which might be effective to treat components of CIS once it has developed, may or may not be useful to prevent the aberrant neurodevelopmental processes which lead to CIS. However, the dosage and duration of treatment necessary to achieve prevention *vs.* amelioration of an established deficit may differ, or, as suggested by Thomases et al. (2013), there may only be certain periods during development when prevention strategies will be effective, or optimally so. The very high doses of a variety of agents needed to prevent the effects of sc PCP to produce deficits in NOR and reversal learning, compared to the doses needed to acutely ameliorate the

effects of scNMDAR antagonists noted previously, suggests the need for studies with high doses of very tolerable drugs at various periods during development.

Cortical and hippocampal DA release and NOR

A candidate for the shared effect of 5-HT$_{2A}$/D$_2$ AAPDs and amisulpride which might mediate the reversal of the effects of sc PCP treatment, is their ability to enhance DA, ACh or glutamate release, or both, in cortex and other brain regions (Ichikawa and Meltzer, 1999; Kuroki et al., 1999). As shown in Fig. 5, lurasidone significantly increases cortical DA, ACh and glutamate efflux, but not that of the inhibitory neurotransmitter, GABA. 5-HT$_{1A}$ agonism also contributes to the ability of AAPDs to increase cortical DA efflux, regardless of their intrinsic 5-HT$_{1A}$ activity, since AAPDs such as olanzapine and risperidone lack intrinsic 5-HT$_{1A}$ receptor agonist activity, but their ability to enhance DA efflux in cortex, or to reverse the effects of sc PCP is also blocked by WAY100635 (Ichikawa et al., 2001). Clozapine, olanzapine and ziprasidone, but not haloperidol, enhanced DA efflux in the PFC of wild-type but not 5-HT$_{1A}$ knockout mice after both systemic and local administration (Diaz-Mataix et al., 2005; Bortolozzi et al., 2010). Local administration of clozapine, olanzapine and risperidone by reverse dialysis increased cortical DA efflux equally in wild-type and 5-HT$_{2A}$R knockout mice. Sulpiride, which shares D$_2$, D$_3$, but not 5-HT$_7$ antagonist properties with amisulpride, enhances cortical DA efflux (Kuroki et al., 1999). Haloperidol, which does not ameliorate the deficit in rats due to sc PCP treatment, had no effect on cortical efflux of any of these four neurotransmitters at the dose studied here, which produces plasma levels comparable to clinical doses (Fig. 5). Tandospirone also enhanced cortical DA, but not ACh, glutamate or GABA release (Fig. 5). WAY 100635, a 5-HT$_{1A}$ antagonist, partially blocked the DA efflux induced by lurasidone and other AAPDs (Ichikawa et al., 2002c; Li et al., 2005; Huang et al., 2012). Other 5-HT$_{1A}$ agonists have also been shown to preferentially augment the release of DA in the PFC (Rasmusson et al., 1994; Wedzony et al., 1996), and increase the bursting activity of DA neurons innervating the PFC (Arborelius et al., 1993; Pessia et al., 1994; Lejeune and Millan, 1998). SB269970 increased DA and 5-HT efflux in the rat PFC (Wesołowska and Kowalska, 2008). Studies of the effect of these agents in rodents which have received sc treatment with PCP, followed by a washout, are in progress.

Increased cortical DA release.has been demonstrated during a variety of cognitive behaviours in rodents, including cognitive behaviours (Giovannini et al., 1998; Phillips et al., 2004; Ihalainen et al., 2010; Guzmán-Ramos et al., 2012; Stanley et al., 2012) and in primates in a working memory task (Watanabe et al., 1997).
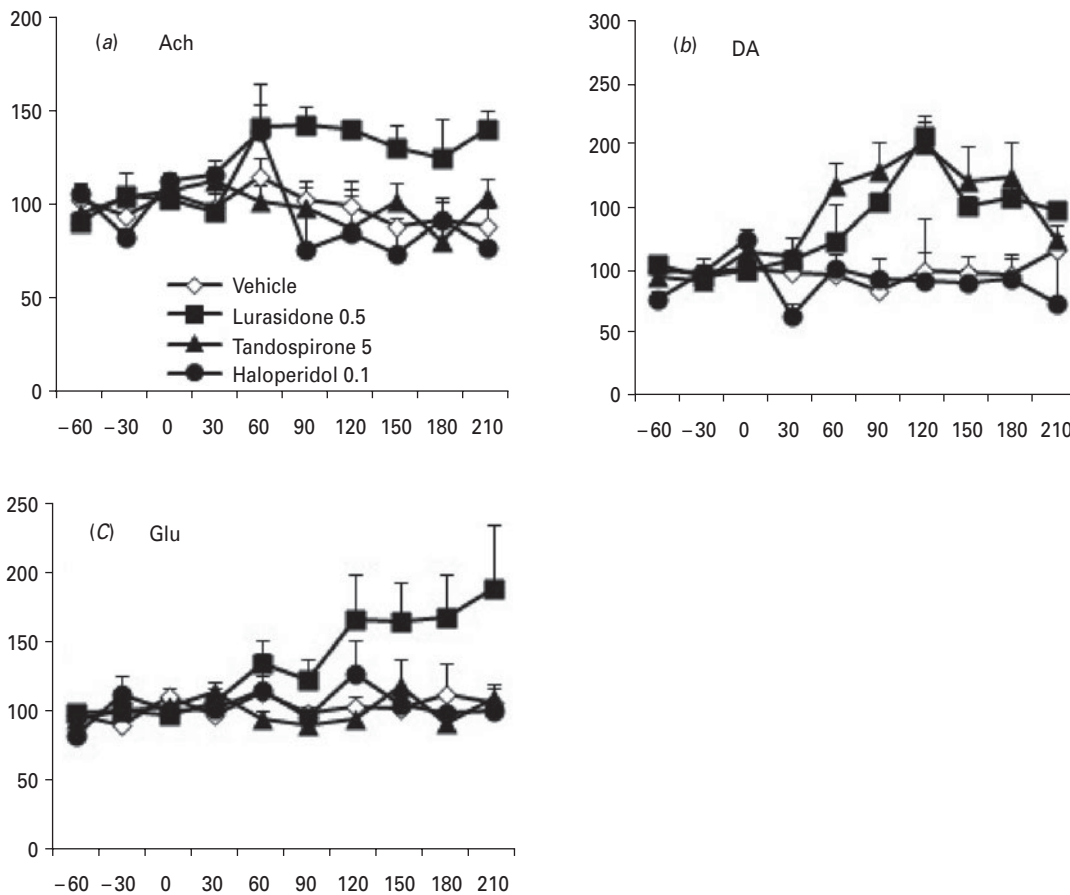
Fig. 5. The effect of lurasidone (0.5 mg/kg, i.p.), tandospirone (5 mg/kg) and haloperidol (0.1 mg/kg) (see Huang et al., 2008 for description of sample collection) on acetylcholine (ACh, A), dopamine (DA, B), glutamate (Glu, C) efflux in the rat mPFC (Huang and Meltzer, in preparation).

D$_1$ DA receptor stimulation

The effect of increased dopaminergic activity in the mPFC and the HIP to restore NOR in the NMDAR-treated rodents is likely mediated by D$_1$ DA receptor stimulation (Hotte et al., 2005; McLean et al., 2009a, b; Horiguchi et al., 2011a). D$_1$ DA receptors are abundant in the mPFC, other cortical regions, and HIP. We have demonstrated that the selective D$_1$ agonist, SKF38393 (0.5–40 mg/kg), is able to reverse the deficit in NOR produced by sc treatment with PCP in an inverted U-shape dose response manner in rats and in C57BL/6J male mice (Horiguchi and Meltzer, 2013; Rajagopal and Meltzer in preparation). The ameliorating effect of SKF38393 on the PCP-induced NOR deficit was blocked by the D$_1$ antagonist, SCH23390, supporting D$_1$ receptor stimulation as the basis for the effect of SKF38393 (Horiguchi et al., 2011a). An inverted U-shape dose response curve was found for SKF38393, as has been observed with other pro-cognitive effects of D$_1$ agonists (Goldman-Rakic et al., 2004). Also, the attenuating effects of the AAPD, asenapine, which has been shown to be a D$_1$ partial agonist,

and aripiprazole, which is not a direct acting D$_1$ agonist (Nagai et al., 2009), were also blocked by the D$_1$ antagonist, SCH23390 (Snigdha et al., 2011). Our results suggest that excessive D$_1$ receptor stimulation may have an adverse effect on declarative memory and possibly other types of cognition in patients with schizophrenia, particularly if a hypoglutamatergic state is present in the brain regions required for declarative memory. Excessive enhancement of DA efflux in the cortex or HIP by AAPDs may be one reason why the AAPDs do not produce a more robust improvement in cognition. Pharmacogenetic studies focused on genes affecting dopamine synthesis, metabolism and signaling may help to guide treatment with these agents (Scharfetter, 2001). Neurotransmitters other than DA are, of course, involved in NOR and other cognitive behaviours. In the NOR test, regardless of object familiarity, object exploration has been found to be accompanied by an increase in hippocampal ACh efflux (Ihalajnen et al., 2010; Stanley et al., 2012). Moreover, glutamate efflux is significantly enhanced on exposure to a novel object (Stanley et al., 2012).

Conclusions

The major goals of an animal model for CIS are to test hypotheses to increase understanding of the pathophysiology of CIS and to develop novel treatments for CIS. An effective model would also provide information that could lead to rejection of claims for effective treatments for CIS that are, or will prove, ineffective. The scNMDAR model of CIS fares moderately well on the first two criteria. If, indeed, schizophrenia is associated with a hypoglutamatergic state and that this provides direction for developing treatments (Coyle et al., 2012), suggesting the need to compensate for the loss of GABAergic interneurons leading to hyperactive glutamatergic pyramidal neurons, the results presented here based upon this model are largely consistent with this line of reasoning. Similarly, the ability of 5-HT$_{1A}$ partial agonists and AAPDs which are direct or indirect 5-HT$_{1A}$ agonists to diminish the activity of pyramidal neurons is supportive of the model developed from the observations of the cognitive disrupting effects of the NMDAR antagonists in healthy individuals and patients with schizophrenia. The consistent superiority of AAPDs over TAPDs to improve cognition in the NMDAR antagonist model, as well as the DISC1 transgenic mouse, suggests that AAPD effects on cognition in schizophrenia provide a powerful test of the utility of these models for identifying potential treatments for CIS for some patients with schizophrenia. At the same time, they indicate that other mechanisms and other animal models will be needed to treat the majority of patients with CIS. However, that should not diminish the importance of the achievement to assist some patients in a clinically meaningful manner.

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