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Glutamatergic Dysfunction in Schizophrenia: *from basic neuroscience to clinical psychopharmacology*

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Abstract

The underlying cellular mechanisms leading to frontal cortical hypofunction (i.e., hypofrontality) in schizophrenia remain unclear. Both hypoactive and hyperreactive prefrontal cortical (PFC) states have been reported in schizophrenia patients. Recent proton magnetic resonance spectroscopy studies revealed that antipsychotic-naïve patients with first-psychotic episode exhibit a hyperactive PFC. Conversely, PFC activity seems to be diminished in patients chronically exposed to conventional antipsychotic treatments, an effect that could reflect the therapeutic action as well as some of the impairing side effects induced by long-term blockade of dopamine transmission. In this review, we will provide an evolving picture of the pathophysiology of schizophrenia moving from dopamine to a more glutamatergic-centered hypothesis. We will discuss how alternative antipsychotic strategies may emerge by using drugs that reduce excessive glutamatergic response without altering the balance of synaptic and extrasynaptic normal glutamatergic neurotransmission. Preclinical studies indicate that acamprosate, a FDA approved drug for relapse prevention in detoxified alcoholic patients, reduces the glutamatergic hyperactivity triggered by ethanol withdrawal without depressing normal glutamatergic transmission. Whether this effect is mediated by a direct modulation of NMDA receptors or by antagonism of metabotropic glutamate receptor remains to be determined. We hypothesize that drugs with similar pharmacological actions to acamprosate may provide a better and safer approach to reverse psychotic symptoms and cognitive deficits without altering the balance of excitation and inhibition of the corticolimbic dopamine-PFC system. It is predicted that schizophrenia patients treated with acamprosate-like compounds will not exhibit progressive cortical atrophy associated with the anti-dopaminergic effect of classical antipsychotic exposure.

Keywords

schizophrenia; antipsychotic drugs; adolescence; NMDA; prefrontal cortex; dopamine; GABA; psychosis

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New and Old Problems in the Treatment of Schizophrenia Symptoms

Since the serendipitous discovery of drugs with antipsychotic properties in the '50s prolonged hospitalizations were no longer necessary for most patients with schizophrenia (Beasley et al., 2006, Freedman, 2005, Meltzer et al., 1990, Wiersma et al., 2000). During the '60s, the discovery of clozapine, an antipsychotic drug exempt from extra-pyramidal side effects, introduced significant improvements in the treatment of this disorder (Hippius, 1989). Later, the demonstration of the unique effectiveness of this drug in refractory psychotic symptoms represented another advance (Kane et al., 1988). However, the emergence of fatal agranulocytosis during the '70s, and the more recent awareness of metabolic side effects (Bustillo et al., 1996, Cohen et al., 1990, Henderson et al., 2000, Lamberti et al., 2006) as well as potentially lethal cases of pancreatitis, myocarditis and polyserositis (Killian et al., 1999, La Grenade et al., 2001, Merrill et al., 2006, Schonfeldt-Lecuona and Connemann, 2002, Wehmeier et al., 2003) associated with chronic exposure to clozapine, fueled the search for clozapine-like drugs not associated with life-threatening side effects. Pursuing this goal, several new antipsychotic drugs have been developed during the last decades. A reduced incidence of extra-pyramidal side effects without inducing agranulocytosis has been demonstrated in patients treated with second-generation drugs (Freedman, 2005, Gardner et al., 2005). However, none of these so-called second-generation antipsychotics have achieved similar efficacy to clozapine (Azorin et al., 2001, Breier et al., 1999, Chakos et al., 2001, Conley et al., 1999, Davis et al., 2003, McEvoy et al., 2006, Shaw et al., 2006). More importantly, increased weight gain, hypercholesterolemia, diabetes and hyperprolactinemia still represent serious side effects associated with chronic exposure to some of these compounds (Kapur et al., 2002, Volavka et al., 2004).

Besides the side effects, current available antipsychotic drugs have shown very limited impact on another core feature of schizophrenia, that is, cognitive and emotional impairments (Carpenter and Gold, 2002, Gardner et al., 2005, Keefe et al., 2006a, Keefe et al., 2006b, Mishara and Goldberg, 2004, Rosenheck et al., 2006). In fact, cognitive deficits are better predictor of the degree of social disability in patients with schizophrenia than the residual psychotic symptoms (Gold et al., 2002, Green et al., 2000, Green et al., 2002, Hyman and Fenton, 2003, Milev et al., 2005, Rosenheck et al., 2006). Likewise, emotional deficits have emerged as another important predictor of disability in these patients (Milev et al., 2005). Thus, the lack of effectiveness of first and second generation antipsychotic drugs on cognitive and emotional deficits in schizophrenia may explain why the long-term prognosis in this psychiatric disorder remains unsatisfactory (Hegarty et al., 1994, Malla and Payne, 2005, Wiersma et al., 2000).

Here, we will review recent evidence supporting an evolving picture of the pathophysiology of schizophrenia moving from dopamine (DA) to a more glutamatergic-centered hypothesis. We will first summarize the limitations of currently available antipsychotic drugs and present evidence indicative of a hyperglutamatergic prefrontal cortex (PFC) underlying psychotic symptoms in schizophrenia. Alternative notions from simple hypofrontality to a more complex developmental dysregulation of prefrontal functioning will be introduced, in particular whether the glutamatergic hypothesis may be best framed as hypo- vs. hyperglutamatergic state. Next, we will discuss how partial NMDA receptor agonists and metabotropic glutamate receptor 5 (mGluR5) antagonists (e.g. acamprosate) may be more effective in treating cognitive deficits associated to schizophrenia by restoring the balance of PFC glutamatergic function. Lastly, we will propose a coherent hypothesis predicting the utility of acamprosate-like compounds as neuroprotective interventions in at-risk adolescents with cognitive and emotional impairments or sub-threshold psychotic symptoms.

Antipsychotic Drugs and Cognitive Symptoms in Schizophrenia

It is well known that current available antipsychotic drugs have limited effect in treating cognitive and emotional impairments in schizophrenia. In fact, cognitive deficits seem to be associated with severe reduction in PFC volume in patients treated with haloperidol (Lieberman et al., 2005b), and the initial cognitive improvement observed after olanzapine (10-20 mg/day) and haloperidol (2-20 mg/day) treatment became no longer apparent after 1 year of drug exposure when detectable reductions in PFC volume emerge (Keefe et al., 2006a, Keefe et al., 2006b, Lieberman et al., 2005a). Similar PFC reductions in gray and white matter were found after 2 years of olanzapine or haloperidol exposure (Dorph-Petersen et al., 2005). Thus, the lack of cognitive improvement could be due to the anatomical and cellular alterations induced by prolonged antipsychotic exposure as these changes seem to be positively correlated with the cumulative doses of antipsychotic exposure (Cahn et al., 2002, Gur et al., 1998).

The mechanisms underlying the anatomical and molecular changes observed after chronic exposure to antipsychotics have yet to be identified. Evidences indicate that these pathophysiological changes could be due to downregulation of neurotrophic factors induced by the anti-DA effect of antipsychotic drugs, in particular by interfering signaling pathways underlying D1 receptor activation. Although it is well established that first and second generation antipsychotic drugs exert anti-DA effects, mainly by targeting D2 over D1 receptors (Creese et al., 1976, Seeman and Lee, 1975), prolonged blockade of D2 receptors can also lead to decreased expression of PFC D1 receptors (Castner et al., 2000, Lidow et al., 1997, Lidow and Goldman-Rakic, 1994). Consequently, chronic exposure to antipsychotic drugs may produce neuronal atrophy in DA-innervated brain areas by disrupting D1-dependent trophic signaling (i.e., protein kinase A -PKA-) on growth and maintenance of new dendritic spines (Lisman and Grace, 2005). Indeed, D1 receptor activation increases surface expression of AMPA receptor subunits in cortical neurons through a PKA-dependent mechanism (Smith et al., 2005, Sun et al., 2005), and alter the strength of synaptic communication induced by long-term potentiation (LTP) (Malenka, 2003), a cellular mechanism for learning and memory (Miles et al., 2005). Similarly, PKA activation facilitate the insertion of brain derived neurotrophic factor (BDNF) receptor tyrosine kinase B (TrkB) into the dendritic spines (Ji et al., 2005), and favors the arrangement of new dendritic spines (Tyler and Pozzo-Miller, 2001). Therefore, D1-mediated PKA signaling may promote the formation of new dendritic spines and synaptic contacts during learning and memory (Jay, 2003, Lisman and Grace, 2005), and disruption of D1 receptor-dependent neurotrophic signaling could explain some of the cellular and synaptic alterations observed after prolonged exposure to antipsychotic drugs (Konopaske et al., 2007): BDNF protein and mRNA levels were reduced in animals chronically exposed to haloperidol (Angelucci et al., 2000, Bai et al., 2003, Chlan-Fourney et al., 2002, Lipska et al., 2001, Pillai et al., 2006b), while downregulation of TrkB receptors in the PFC was correlated with the duration and doses of antipsychotic treatment in schizophrenia patients (Weickert et al., 2005). Overall, these results indicate that first and second generation antipsychotic drugs may alter cortical levels of neurotrophic factors by antagonizing DA signaling.

On the other hand, it has been proposed that the progressive cortical atrophy observed in schizophrenia patients with first psychotic episode could be triggered by psychosis itself (Lieberman, 1999, Lieberman et al., 2001, Lieberman et al., 2005b), whereas the delayed anatomical changes found in olanzapine-treated patients reflect a pro-neurotrophic effect that counter-balance the effect of first psychotic episode-induced neurotoxicity (Lieberman et al., 2005a, Lieberman et al., 2005b). However, neuropathological and gene expression studies aimed to support the existence of first psychosis-induced neurotoxicity have yielded negative results (Benes et al., 2006, Benes et al., 2003, Damadzic et al., 2001, Harrison, 1999). Some studies found reduction of BDNF expression (Lipska et al., 2001) whereas no change (Pillai

et al., 2006a) or even increased levels of BDNF were observed after chronic exposure to olanzapine and clozapine (Bai et al., 2003). A likely explanation for these contrasting results may be the duration of antipsychotic exposure. For example, it is well known that acute administration of second-generation antipsychotic drugs increases DA release in the medial PFC (Diaz-Mataix et al., 2005, Ichikawa et al., 2002, Li et al., 2005, Li et al., 2004, Li et al., 2003), an effect that could potentially lead to higher levels of BDNF (Bai et al., 2003). In contrast, 180 days treatment with olanzapine showed no major effects on BDNF protein levels, but decreased significantly the activity and the levels of the neuroprotective enzyme manganese-superoxide dismutase in the cortex (Pillai et al., 2006a, Pillai et al., 2006b). Similarly, a reduction of cortical gray and white matter was observed after two years of olanzapine treatment in non-human primates (Dorph-Petersen et al., 2005). Interestingly, similar anatomical changes in the PFC were observed after twelve but not six-month exposure to olanzapine in schizophrenia patients exhibiting first psychotic episode (Lieberman et al., 2005b). Taken together, these findings suggest that prolonged treatments with second-generation antipsychotic drugs may alter PFC structure and function. Consistent with this hypothesis, a progressive decline in cognitive performance in a group of 80 schizophrenia patients (many of them treated with olanzapine or clozapine) was observed only after a two-year period of antipsychotic exposure (Andreasen et al., 2005). Studies exploring whether prolonged exposure to second generation antipsychotic drugs increase DA release in the PFC may shed some light on the mechanisms underlying the delayed cortical atrophy and cognitive deterioration associated with chronic exposure to antipsychotics. New therapeutic strategies with better neuroprotective and neurocognitive profiles need to be examined, particularly in first psychotic episode patients.

New Hypothesis for Addressing New Problems

Growing evidence indicates that abnormalities in glutamatergic neurotransmission may underlie some of the core psychopathological phenomena observed in schizophrenia (Harrison and Weinberger, 2005). The glutamatergic hypothesis of schizophrenia was originally based upon clinical observations of chronic abusers of the NMDA receptor antagonist phencyclidine (PCP). Similar to the symptoms observed in schizophrenia, PCP exposure elicits thought disorder, emotional blunting, working memory disturbances and auditory hallucinations (Javitt and Zukin, 1991, Luby et al., 1959). The observation that acute administration of another NMDA receptor antagonist, that is, sub-anesthetic doses of ketamine, induces similar psychopathological effects in healthy volunteers (Adler et al., 1999, Krystal et al., 1994, Malhotra et al., 1996) supported the hypothesis that hypofunctional NMDA receptors may play a critical role in the pathophysiology of schizophrenia. Consequently, anti-DA drugs combined with agents that enhance NMDA function might ameliorate the residual cognitive, emotional and psychotic symptoms in schizophrenia (Goff and Coyle, 2001, Goff et al., 1999). However, a recent multicentric study failed to provide evidence in favor of this therapeutic intervention (Carpenter and Thaker, 2007).

A re-formulation of the glutamatergic hypothesis of schizophrenia has emerged. According to this new paradigm, hyperactive glutamatergic neurons in several brain regions including the PFC may underlie the psychotic, cognitive and emotional manifestations in schizophrenia (Krystal et al., 2003, Moghaddam, 2003). Several pieces of converging evidence have contributed to establish this reformulation: 1) Microdialysis studies showing that glutamate levels are increased in the striatum (Bustos et al., 1992) and PFC (Moghaddam et al., 1997) of animals acutely treated with psychotomimetic doses of NMDA antagonists; 2) Behavioral studies showing that hyperlocomotion and working memory impairments induced by PCP are correlated with increased glutamate levels in the PFC (Adams and Moghaddam, 1998); 3) Pharmacological studies showing that glutamate release inhibitors such as lamotrigine (Anand et al., 2000) and mGluR 2 agonists (Moghaddam and Adams, 1998) ameliorate the cognitive

and behavioral abnormalities induced by acute exposure to psychotomimetic doses of NMDA antagonists; 4) *In vivo* electrophysiological recordings in freely moving animals revealing that acute administration of NMDA antagonists is associated with PFC pyramidal neurons excitation (Jackson et al., 2004), an effect that could be triggered by an increased tonic excitatory inputs from the ventral hippocampus (Jodo et al., 2005); 5) *In vitro* electrophysiological studies showing that hippocampal GABAergic interneurons that control pyramidal neuron firing are particularly sensitive to psychotomimetic doses of NMDA antagonists (Grunze et al., 1996); 6) Neuroimaging studies indicating that psychotic symptoms and cognitive abnormalities elicited by acute administration of ketamine in healthy volunteers concur with an enhancement of PFC metabolic activity (Breier et al., 1997, Holcomb et al., 2005, Holcomb et al., 2001); 7) Proton magnetic resonance spectroscopy studies showing that glutamine levels, an indicator of synaptic glutamate recycling activity (Rothman et al., 1999), are increased in the medial PFC of healthy volunteers acutely exposed to sub-anesthetic doses of ketamine (Rowland et al., 2005), antipsychotic naïve first psychotic episode schizophrenia patients (Bartha et al., 1997, Theberge et al., 2002), and adolescents at-risk of developing schizophrenia (Tibbo et al., 2004). Thus, despite binding at different receptors in dendritic spines, psychotomimetic drugs such as LSD, amphetamine and PCP may trigger signal transduction pathways that converge to potentiate glutamatergic excitability via inhibition of protein phosphatase 1, an enzyme that normally downregulates excitatory synapses (Svenningsson et al., 2003). At the network level, psychotomimetic doses of NMDA antagonist may favor the balance of excitation over inhibition by blocking NMDA-dependent excitatory inputs to GABAergic interneurons. Overall, these results indicate that a dysfunctional enhancement of cortical excitatory transmission maybe the common synaptic effect of psychotomimetic drugs that induced schizophrenia-like symptoms.

How a primary dysregulation of glutamatergic neurotransmission may explain the fact that most cases of schizophrenia emerge after puberty?

Electrophysiological recordings of PFC pyramidal neurons at different maturational stages have revealed that DA-glutamate interactions in the PFC mature after puberty (Tseng and O'Donnell, 2004, Tseng and O'Donnell, 2005). Therefore, a cortical disruption of NMDA function may contribute to establish the pathophysiological changes observed in schizophrenia by altering the acquisition of mature DA responses in the PFC. For example, glutamatergic plateau depolarizations induced by co-activation of NMDA and D1 receptors is developmentally regulated in a manner that a D1-dependent enhancement of NMDA function in the PFC can be observed only in post-pubertal, but not pre-pubertal animals (Tseng and O'Donnell, 2005). This is consistent with previous studies showing a delayed acquisition of adult levels of DA receptors (Leslie et al., 1991, Tarazi et al., 1999) and NMDA receptor subunits (Monyer et al., 1994, Williams et al., 1993) around puberty. Furthermore, the expression of BDNF mRNA, which is tightly dependent on the activation of intra-synaptic NMDA receptors (Hardingham et al., 2002), reaches its maximum level in the PFC during late adolescence and young adulthood (Webster et al., 2002). Thus, subtle changes in glutamatergic excitability determined by genetic and environmental factors may drive some of the mild cognitive, emotional and motor abnormalities observed in pre-psychotic children and adolescents (Lewis and Levitt, 2002, Lewis and Murray, 1987, Murray and Waddington, 1990, Weinberger, 1987). These changes may remain relatively silent until the acquisition of mature cognitive abilities dependent on D1-NMDA interactions that emerge around puberty (Tseng and O'Donnell, 2005). A developmental disruption of either or both the glutamatergic and the DA systems may therefore lead to the cognitive and emotional manifestations of prodromal schizophrenia (Lencz et al., 2006, Reichenberg et al., 2005, Weiser et al., 2001). Without treatment, post-pubertal hyperglutamatergic states may escalate until full psychotic episodes emerge during late adolescence and early adulthood.

The Glutamatergic Hypothesis for Psychosis: *addressing the objections*

Could the hyperglutamatergic neurotransmission, exacerbated by an abnormal D1-NMDA co-activation during late adolescence underlie the core of early pathophysiological events in schizophrenia?

This hypothesis may appear at odds by the fact that antipsychotic drugs have been shown to target mainly D2 over D1 receptors (Tauscher et al., 2004). If an exaggerated PFC D1-NMDA-dependent excitation plays a role in psychosis, it may seem unlikely that D2 antagonists would exert any antipsychotic effects. However, it is well known that prolonged exposure to D2 antagonists are typically associated with a series of changes including downregulation of PFC D1 receptors (Castner et al., 2000, Lidow et al., 1997, Lidow and Goldman-Rakic, 1994) and DA cell firing (Bai et al., 2003, Boye and Rompre, 2000, Bunney and Grace, 1978, Di Giovanni et al., 1998, Grace et al., 1997, Moore et al., 1998), which in turn may decrease DA synthesis (Grunder et al., 2003) and impair prefrontal D1-dependent functioning. On the other hand, it has been documented that some of the behavioral effects of DA are dependent on co-activation of D1 and D2 receptors within the cortico-basal ganglia loop (Kita et al., 1999, Waszczak et al., 2002). Both D1 and D2 DA receptors are co-expressed in single striatal neurons and their co-activation can lead to calcium release from internal stores (Aizman et al., 2000, Lee et al., 2004, So et al., 2005) and increase neuronal activity (Hopf et al., 2003). It is possible that D2 antagonists prevent D1 mediated potentiation of NMDA response within the PFC by decreasing the D2-dependent calcium release from internal stores. Although this hypothesis awaits confirmation in cortical neurons, it seems likely that chronic blockade of D2 receptors could ultimately compromise cognitive performance by disrupting PFC D1-dependent signaling.

Why selective D1 antagonists failed to elicit significant therapeutic effects in schizophrenia?

Several factors may explain the lack of effectiveness of selective D1 antagonists in treating symptoms associated to schizophrenia (de Beaufort et al., 1995, Den Boer et al., 1995, Karlsson et al., 1995). First, the therapeutic effects of D1 antagonists were initially tested in patients exposed to prolonged antipsychotic drugs treatment, a stage where there hyperglutamatergic state may not longer present in the PFC (Bartha et al., 1997, Theberge et al., 2002, Tibbo et al., 2004). Secondly, it has been suggested that a proper balance of PFC D1 receptor activation (i.e., invert U curve) is required for supporting optimal working memory performance (Arnsten and Li, 2005). Several studies have also highlighted the need of DA-glutamate co-activation for a number of prefrontal functions including appetitive instrumental learning, memory retrieval and enhancement of hippocampal-PFC synaptic plasticity (Baldwin et al., 2002, Gurden et al., 1999, Jay, 2003). Thus, potent D1 antagonists may not only reduce the hyperglutamatergic state but also impair PFC functioning in schizophrenia. Two trials using full D1 antagonists have to be aborted as result of the emergence of severe psychosis exacerbation (de Beaufort et al., 1995, Karlsson et al., 1995).

Finally, it is not clear whether cognitive and emotional deterioration putatively driven by chronic hypoglutamatergic states are the result of prolonged antipsychotic exposure since similar deficits were reported in schizophrenia subjects before the introduction of anti-DA drugs (Kraepelin, 1919; Bleuler, 1911). It has been documented that chronic exposure to low doses of NMDA antagonist significantly decrease PFC DA and glutamate turnover (Jentsch and Roth, 1999, Kondziella et al., 2005) and elicit PFC-related behavioral deficits resembling the cognitive deterioration observed in chronic stages of schizophrenia (Jentsch et al., 1997, Jentsch and Roth, 1999). Taken together, these findings suggest that repetitive episodes of hyperglutamatergic activity may trigger compensatory mechanisms that would in turn downregulate PFC excitatory transmission. Thus, even in the absence of D2 antagonists, a hypoglutamatergic PFC may emerge resulting from repetitive untreated hyperglutamatergic state as seen after chronic exposure to PCP.

In summary, it is possible that the emergence of an abnormal PFC D1-NMDA co-activation during late adolescence could exacerbate the hyperglutamatergic state that underlies the early pathophysiological events in schizophrenia. If the model proposed here capture at least part of what is really occurring in early stages of schizophrenia, we predict that the earlier the introduction of non-DA therapeutic interventions, the higher the probability of preventing compensatory changes associated with a hypoactive PFC.

Cellular Mechanisms Underlying the Hyperglutamatergic State

Several DA-dependent and DA-independent factors could contribute to elicit the hyperactive NMDA state in schizophrenia. At cellular level, an increase expression of calcyon (Koh et al., 2003), a D1 receptor interacting protein that allows calcium release from internal stores (Bergson et al., 2003), may potentiate NMDA function in a manner independent from D2 receptor activation. Similarly, reduction of calcineurin levels (Eastwood et al., 2005, Gerber et al., 2003), a phosphatase that normally reduces the excitability of NMDA receptors (Rycroft and Gibb, 2004, Smith et al., 2006), may also enhance NMDA function and promote working memory deficits in response to low doses of the NMDA antagonist MK801 (Miyakawa et al., 2003). Furthermore, a reduced expression of the RSG4 gene (Chowdari et al., 2002, Erdely et al., 2006, Prasad et al., 2005, Saugstad et al., 1998), which encodes a protein product that normally decreases the activation of mGluR5, may result in over-activation of NMDA receptors. This change at mGluR5 function might ultimately increase PFC pyramidal neurons bursting activity through an NMDA-dependent mechanism (Homayoun et al., 2004). Finally, a recent study has identified a genetic defect affecting the expression of the phosphodiesterase 4B gene (PDE4B) in schizophrenia and mood disorders. This gene product plays a critical role in maintaining the normal D1-dependent protein kinase A signal transduction pathway. More importantly, it was found that the PDE4B enzyme interacts with the disrupted in schizophrenia 1 (DISC 1) gene in a manner that PDE4B can be released from DISC 1 when the dendritic levels of cyclic adenosine monophosphate (cAMP) are elevated (Millar et al., 2005). Thus, abnormalities in the expression or activity of different gene products such as calcyon, calcineurin, PDE4B and DISC 1 may lead to hyper-excitability signal transduction pathways dependent on D1-NMDA receptor activation.

Disruption of GABAergic interneurons function may also contribute to initiate and sustain a hyperglutamatergic state in schizophrenia. PFC GABAergic interneurons play an important role in determining the responses of pyramidal neurons to glutamatergic and DA inputs (Tseng et al., 2006b, Tseng and O'Donnell, 2004, Tseng and O'Donnell, 2007a, Tseng and O'Donnell, 2007b) and functional disruption of this selective neuronal population could ultimately lead to the altered cognitive performances observed in schizophrenia (Lewis et al., 2005). Because DA-dependent attenuation of PFC NMDA responses involves activation of local GABAergic interneurons (Tseng and O'Donnell, 2004), a reduction of this inhibitory tone may also contribute to trigger and sustain the hyperglutamatergic state in the PFC. Although an overall enhancement of PFC activity may appear at odds with the traditional concept of hypofrontality (Manoach, 2003), recent studies conducted in a developmental animal model that exhibits cortical deficits resembling to those observed in schizophrenia indicate that the hypofrontal state could be associated with an hyperactive PFC. The characteristic post-pubertal emergence of PFC glutamatergic hyperactivity (O'Donnell et al., 2002, Tseng et al., 2007) and hyperreactive PFC metabolic response to mesocortical stimulation (Tseng et al., 2006a) are correlated with a selective down regulation of PFC glutamate decarboxylase-67 mRNA, a neuronal marker for GABA interneurons (Lipska et al., 2003). Furthermore, a postpubertal disruption of D2 receptor function that normally regulate PFC excitatory responses through several pre- and postsynaptic mechanisms (Tseng and O'Donnell, 2004, Tseng and O'Donnell, 2007a) combined with an abnormal response to D1 activation may also serve to increase pyramidal neurons excitability to NMDA (Tseng et al., 2007) and yield the concurrent hyper-

reactive and hypofunctional state in the PFC (Tseng et al., 2006a). Finally, it is also possible that other monoamines may potentiate this abnormal enhancement of NMDA function, particularly the cortical norepinephrine system. Stress-dependent increases of norepinephrine release sustaining the hyperactive NMDA state through activation of $\alpha 1$ adrenergic receptors and upregulation of postsynaptic protein kinase C signaling pathways in the PFC (Arnsten, 2004) may underlie the hyperreactive response to stress observed in schizophrenia.

In summary, cortical deficits in schizophrenia (i.e., hypofrontality) could be therefore compounded by a hyperglutamatergic PFC state elicited by a reduction of PFC GABAergic function concurrent with a disruption of D2 modulation and an abnormal potentiation of D1 and NMDA-mediated responses. These two pathophysiological conditions are not mutually exclusive and may not be restricted to the PFC since markers of increased glutamatergic activity dependent on NMDA receptors concurs with those indicative of decreased GABAergic function such as of GAD-67, GAD-65 and GAT1 in the cerebellar cortex of patients with schizophrenia (Paz et al., 2006).

Searching for New Psychopharmacological Targets to Restore the Balance of Glutamatergic Neurotransmission: *a lesson from acamprosate*

Acamprosate is a derivative of the amino acid taurine and despite its low intestinal absorption, it has been used for more than two decades in Europe to prevent relapse in alcoholic patients (Buonopane and Petrakis, 2005, Room et al., 2005, Williams, 2005). Recently, the FDA approved the use of acamprosate for detoxified alcohol-dependent patients in USA. Although its mechanism of action has not been completely identified, preclinical studies suggest that acamprosate normalizes glutamate release and NMDA receptors function without altering the normal glutamatergic neurotransmission (De Witte et al., 2005). Several cellular mechanisms may account for the therapeutic effect of acamprosate, particularly by interfering mGluR5-dependent regulation of glutamate release (De Witte et al., 2005). Metabotropic GluR5 is an excitatory G-protein coupled receptor located at both pre- and postsynaptic sites of glutamatergic synapses as well as in glia and astrocytes (Swanson et al., 2005). Activation of presynaptic mGluR5 facilitates synaptic glutamate release whereas postsynaptic mGluR5 increase neuronal excitability by facilitating NMDA currents. Consequently, a reduction of the hyperglutamatergic PFC state could be achieved with acamprosate by attenuating the excitatory effect of mGluR5 on presynaptic glutamate release and by decreasing NMDA-dependent postsynaptic excitability. On the other hand, mGluR5 also regulates non-synaptic release of glutamate from glia and astrocytes via stimulation of the cystine-glutamate antiporter (Xc-) (Melendez et al., 2005, Moran et al., 2005). The Xc- is a non-vesicular transporter that mediates sodium-independent exchange of one intracellular glutamate for one extracellular molecule of cystine, and is responsible for around 50 to 70 % of basal extracellular glutamate in the nucleus accumbens (Baker et al., 2002), but not in the PFC (Melendez et al., 2005). In the PFC, however, Xc- stimulation increases the concentration of non-synaptic, extracellular glutamate, and reduces excitatory synaptic transmission resulting from activation of the inhibitory presynaptic mGluR2/3 (Moran et al., 2005). Accordingly, acamprosate would prevent activation of the Xc- antiporter by antagonizing mGluR5, which in turn would reduce the non-synaptic extracellular glutamate levels and remove the presynaptic mGluR2/3-dependent inhibitory tone at glutamatergic synapses. Removing the mGluR2/3-dependent inhibitory tone on glutamate release might actually contribute to balance the decrease in glutamatergic synaptic transmission induced by presynaptic mGluR5 blockade. It is predicted that by acting on both synaptic and non-synaptic mechanisms underlying glutamate release and its interactions with postsynaptic NMDA receptors, acamprosate-like compounds may restore PFC hyperglutamatergic state without altering the balance of excitatory neurotransmission

Acamprosate also binds the spermidine site of NMDA receptors (Mayer et al., 2002, Naassila et al., 1998) and it is thought to exert a partial agonistic effect acting as an agonist or antagonist depending on the activity of NMDA receptors. For example, acamprosate potentiates the excitatory action induced by low concentration of NMDA and reduced the excitatory effect elicited by higher concentrations of NMDA (Pierrefiche et al., 2004). Accordingly, studies in hyperglutamatergic mutant mice (a rodent model of increased alcohol consumption) revealed that acamprosate normalize glutamate levels and ethanol intake without affecting glutamate levels of control animals (Spanagel et al., 2005). A similar effect was observed in the hippocampus of ethanol-withdrawn rats treated with acamprosate as compared to control animals (Room et al., 2005). Because repetitive exposure to ethanol and withdrawal increases glutamatergic transmission and glutamate release (De Witte, 2004, Krystal et al., 2003), the increased glutamate would reach the extrasynaptic space, which in turn would stimulate more mGluR5 receptors and cause even more glutamate release and abnormal NMDA activation (De Witte et al., 2005). Therefore, acamprosate may effectively block this vicious cycle by normalizing and restoring the balance of glutamatergic neurotransmission across several brain regions through its combined action on mGluR5 and NMDA receptor functions. Furthermore, the increased ethanol intake observed in the hyperglutamatergic mice (Spanagel et al., 2005) raises the intriguing possibility that similar exacerbated glutamatergic condition may be driving, at least in part, the increased prevalence of ethanol abuse and dependence observed in schizophrenia. Interestingly, glutamate-dependent neurotoxicity induced by acute exposure to intermediate doses of NMDA antagonists could be prevented by ethanol exposure in rats (Farber et al., 2004).

Overall, it is tempting to speculate that the modulatory action of compounds that block mGluR5 and exert a partial agonistic effect on NMDA receptors (e.g., acamprosate-like compounds and possibly others) could provide a much better result in restoring altered glutamatergic neurotransmission than that produced by NMDA agonists and antagonists, and that obtained with D2 antagonists, in particular during early stages of the disorder.

Advantages of Using Acamprosate-like Drugs in Prodromal Stages of Schizophrenia

It has been proposed that anti-DA treatments during the early stages of first-episode psychoses may be effective to prevent cognitive and emotional decline in schizophrenia (Lieberman, 1999, Wyatt, 1991). However, recent studies indicate that this strategy does not truly improve the cognitive and emotional outcomes (Ho et al., 2003, Hoff et al., 2000, Marshall et al., 2005, Perkins et al., 2005, Rund et al., 2004), perhaps because cognitive deficits in schizophrenia occurs during late adolescence, before the emergence of psychotic episodes (Perkins et al., 2005). In fact, several retrospective studies have found that cognitive and emotional deterioration in a subgroup of schizophrenia patients become evident when post-pubertal social and cognitive performances are compared with those exhibited in prepubertal ages (Ang and Tan, 2004, Cosway et al., 2000, Fuller et al., 2002, Rabinowitz et al., 2002, Reichenberg et al., 2005, van Oel et al., 2002). Although limited by their retrospective nature, these studies are consistent with the idea that profound changes occurring in the adolescent brain make this neural development period vulnerable. Accelerated pruning of redundant connections in the PFC occurs during this developmental stage (Bourgeois et al., 1994, Huttenlocher, 1979, Huttenlocher and Dabholkar, 1997, Zecevic et al., 1989, Zecevic and Rakic, 1991), while the myelination of axons projecting from the PFC is particularly intense during adolescence and young adulthood (Giedd et al., 1999, Gogtay et al., 2004, Jernigan et al., 1991, Paus et al., 1999, Sowell et al., 2003, Sowell et al., 1999, Toga et al., 2006). Since these events are probably dependent on plastic changes affecting the glutamatergic (Monyer et al., 1994, Williams et al., 1993) and the DA systems (Leslie et al., 1991, Tarazi et al., 1999), it is not surprising that PFC pyramidal neuron response to DA acquire a mature profile

at early postpubertal stages of neural development (Tarazi et al., 1999, Tseng et al., 2006a, Tseng and O'Donnell, 2005, Tseng and O'Donnell, 2007a, Tseng and O'Donnell, 2007b). A similar delayed acquisition of mature responses to DA has been recently observed in PFC interneurons (Tseng and O'Donnell, 2007a, Tseng and O'Donnell, 2007b). All these interactions will ultimately determine the normal balance of excitation and inhibition that is needed for optimal cognitive performances including those dependent on PFC functioning during adulthood. Thus, several abnormalities at cellular and network levels compromising both glutamatergic and GABAergic systems may produce dramatic effects during critical periods of neural development that could potentially lead to permanent loss of synaptic connections resulting in cognitive and emotional alterations in adulthood. Consequently, acute exposure to low doses of NMDA antagonists induces psychotic symptoms and cognitive dysfunctions in pubertal/postpubertal rather than prepubertal ages (Olney and Farber, 1995).

Modulation of glutamatergic neurotransmission within the mesocorticolimbic-PFC network by drugs acting on metabotropic and NMDA glutamate receptors may allow a better control of persistent hyperglutamatergic states that are not affected by D2 receptor blockade. In this regard, it is appealing that clozapine binds D1 receptors with a higher affinity than D2 receptors (Chou et al., 2006, Tauscher et al., 2004). Therefore, clozapine may exert a more direct interaction with NMDA receptors than other antipsychotic drugs, in particular if the hyperglutamatergic state is exacerbated by an abnormal PFC D1-NMDA co-activation. In fact, the response to clozapine can be predicted by polymorphisms within the D1 receptor gene in schizophrenia subjects. Patients with the 2,2, but not with the 1,2 D1 genotype exhibited decrements in psychotic symptoms after clozapine treatment, a therapeutic effect associated with a reduction in PFC metabolism that was not observed in the 1,2 D1 group (Potkin et al., 2003). Furthermore, prolonged clozapine exposure (i.e., 21 days) decreased NMDA-dependent synaptic function (i.e., LTP) (Gemperle and Olpe, 2004). Thus, the therapeutic effects of clozapine in patients with refractory psychotic symptoms might be obtained by decreasing the abnormal PFC D1-NMDA-dependent excitation.

A narrow window of NMDA activation mediated by D1 receptors and α adrenergic receptors is needed to maintain appropriate working memory performance. An excessive stimulation of D1 receptors lead to cognitive dysfunction (Arnsten and Goldman-Rakic, 1998, Cai and Arnsten, 1997, Zahrt et al., 1997) whereas insufficient recruitment of these receptors is associated with working memory deficits (Castner et al., 2000, Sawaguchi and Goldman-Rakic, 1994). Interestingly, a similar inverted U-shape response has been reported for noradrenergic manipulations (Arnsten and Li, 2005). Therefore, drugs with anti-mGluR5 and partial NMDA agonist properties (e.g., acamprosate) might produce better outcomes in patients with severe cognitive dysfunction. Along with this hypothesis, transgenic mice overexpressing D2 receptors in the striatum exhibit severe deficits in working memory-dependent tasks in association with increased D1 receptor responses in the PFC (Kellendonk et al., 2006). Decreasing the expression of D2 receptors in the striatum failed to restore the increased PFC response. This suggests that blocking D2 receptors in the striatum does not prevent working memory impairments secondary to neurodevelopmentally-induced abnormalities of D1-NMDA interactions within the PFC. Thus, direct modulation of hyperactive NMDA receptors by drugs like acamprosate may allow targeting microcircuits within the mesocortico-PFC that are not accessible to conventional D2-based treatments.

Because suicide is a major cause of mortality in schizophrenia and a risk factor for young adults, a note of caution should be mentioned concerning the use of acamprosate in alcoholic patients with suicidal ideation and suicide attempts. Although infrequent, acamprosate seems to induce a relatively higher risk of suicidal thoughts and attempted suicide (2.4 %) when compared to placebo (0.8 %) (2005, Bouza et al., 2004, Chick et al., 2000, Sher, 2006a). However, the incidence of completed suicide in patients receiving acamprosate (0.13 %)

resembled to that observed in the placebo group (0.10 %) (http://www.frx.com/pi/campral_pi.pdf). Because many of these suicidal-related events occurred in the context of alcohol dependence and relapse, the relationship between acamprosate and the emergence of suicidality remains unclear (Sher, 2006b).

Summary and Conclusions

Overall, it becomes clear that the vulnerability of the periadolescence brain to environmentally and genetically driven events that could potentially disrupt the balance of excitation and inhibition in cortical circuits should be taken into consideration when planning psychopharmacological treatments in at-risk adolescent patients exhibiting cognitive and emotional deterioration. Drugs with similar acamprosate-like profile on metabotropic glutamate (e.g., mGluR5) and NMDA receptors may provide a better and safer therapeutic strategy for early stages schizophrenia as compared to risperidone (McGorry et al., 2002), olanzapine (McGlashan et al., 2006, McGlashan et al., 2003) or D-cycloserine (Buchanan et al., 2007). The development of drugs that restore the hyperglutamatergic state by virtue of normalizing the abnormal NMDA function without altering the balance of synaptic and extrasynaptic glutamatergic transmission may be useful for schizophrenia patients with persistent and residual psychotic symptoms as well as cognitive and emotional deficits.

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