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Insights on current and novel antipsychotic mechanisms from the MAM model of schizophrenia

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Abstract

Current antipsychotic drugs (APDs) act on D₂ receptors, and preclinical studies demonstrate that repeated D₂ antagonist administration downregulates spontaneously active DA neurons by producing overexcitation-induced inactivation of firing (depolarization block). Animal models of schizophrenia based on the gestational MAM administration produces offspring with adult phenotypes consistent with schizophrenia, including ventral hippocampal hyperactivity and a DA neuron overactivity. The MAM model reveals that APDs act differently in a hyperdopaminergic system compared to a normal one, including rapid onset of depolarization block in response to acute D₂ antagonist administration and downregulation of DA neuron population activity following acute and repeated D₂ partial agonist administration, none of which are observed in normal rats. Novel target compounds have been developed based on the theory that glutamatergic dysfunction is central to schizophrenia pathology. Despite showing promise in preclinical research, none of the novel drugs succeeded in clinical trials. However, preclinical research is generally performed in normal, drug-naïve rats, whereas models with disease-relevant pathology and prior APD exposure may improve the predictive validity of preclinical research. Indeed, in MAM rats, chronic D₂ antagonist treatment leads to persistent DA supersensitivity that interferes with the response to drugs that target upstream pathology. Moreover, MAM rats revealed that the peri-pubertal period is a stress-sensitive window that can be targeted to prevent the development of MAM pathology in adulthood. Neurodevelopmental models, such as the MAM model, can thus be used to test potential pharmacotherapies that may be able to treat schizophrenia in early stages of the disease.

1. Introduction

Animal models are essential for generating predictions and confirming causal relationships about the development, pathophysiology, and treatment of psychiatric disorders. The value

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CONFLICT OF INTEREST

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of a given model is traditionally based on validity criteria, which consist of face validity (phenotypes that resemble the human condition), construct validity (similar theoretical rationale, such as a common etiology), and predictive validity (the ability to extrapolate the effects of a manipulation between species). An inherent challenge to validity criteria in translational schizophrenia research is the inability to reproduce all dimensions of a uniquely human condition. Current models are thus limited to a subset of phenotypes, with no effective means to directly measure subjective mental states, such as hallucinations and delusions (Arguello and Gogos, 2006; Powell and Miyakawa, 2006).

Despite their limitations, animal models are necessary tools for preclinical research into the mechanism of action and targeting of antipsychotic drugs (APDs). APDs are the primary treatment for schizophrenia and they dramatically reduce psychotic symptoms in many patients (Leucht et al., 2009). However, their therapeutic value is hindered by numerous side effects, limited efficacy across symptom domains, and failure to treat the disease pathology, which can lead to a lifetime of maintenance treatment (Lieberman et al., 2005; Leucht et al., 2012). These factors negatively impact quality of life and contribute to a high level of treatment nonadherence that typically results in relapse (Robinson et al., 2002; Lieberman et al., 2005). Current APDs are also unable to address heterogeneity, both between individuals with distinct pathologies (Demjaha et al., 2014; Howes and Kapur, 2014) and within an individual through different phases of the disease (Krystal and Anticevic, 2015). Novel pharmacological targets have been investigated based on theories largely generated from animal research, yet clinical trial results have been less than promising (Dunlop and Brandon, 2015). The apparent lack of predictive validity, as evidenced by the failed clinical trials, necessitates reevaluation of the rigor and design of preclinical research for the future development of novel therapies. Similarly, clinical trial design should be re-evaluated based on data emerging from preclinical studies. Current efforts must be aimed at investigating potential variables that contribute to this disconnect to improve the translation of animal models and the therapeutic value of pharmaceutical treatments.

2. Modeling dopamine dysfunction in schizophrenia

2.1 Clinical evidence of dopamine dysfunction in schizophrenia

The success of the first APD chlorpromazine in the 1950s was a breakthrough in the current era of pharmacotherapy and represented a shift in the conceptualization of psychiatric symptoms as biological constructs that can be targeted and treated (López-Munoz et al., 2005). In the decade following their established efficacy, it was suggested that APDs may work by acting on dopamine (DA) receptors (Carlsson and Lindqvist, 1963; Van Rossum, 1967). This was later confirmed by the finding that all APDs block D₂ receptors, which is strongly linked to their antipsychotic effect (Seeman and Lee, 1975; Creese et al., 1976). Action at D₂ receptors has since been proposed to be both necessary and sufficient for the therapeutic effect of current APDs on positive symptoms (Kapur and Remington, 2001).

The DA hypothesis of schizophrenia postulates that hyperactivity of the DA system drives psychotic symptoms. Patients with schizophrenia who respond to current treatments consistently demonstrate measures of increased presynaptic DA function compared to healthy controls (Howes et al., 2012). Early pivotal studies in patients used positron

emission tomography (PET) and single photon emission computed tomography (SPECT) imaging to examine radioligand displacement from DA receptors as a measure of DA release. Compared to healthy controls, patients with schizophrenia show increased release of DA in the striatum at basal conditions (Abi-Dargham et al., 2000) and in response to amphetamine (Laruelle et al., 1996; Abi-Dargham et al., 1998). Furthermore, the increased DA signal is correlated with positive symptom severity (Laruelle et al., 1999). Patients with schizophrenia also show elevated striatal DA synthesis capacity, measured by fluorodopa uptake into DA terminals. The increased response capacity of the DA system is present in individuals at ultrahigh risk for psychosis (UHR), with further increase associated with the onset of psychosis (Howes et al., 2009; Howes et al., 2011a; Howes et al., 2011b). Although measures of DA function are reliable markers of psychosis in patients, there are challenges associated with choosing appropriate animal models to best study DA dysfunction relevant to schizophrenia.

2.2. Animal models of dopamine dysfunction

2.2.1. Pharmacological models of schizophrenia—Pharmacological models of schizophrenia are based on studying the action of drugs that induce psychotic states. For example, NMDA receptor antagonists, including phencyclidine (PCP) and ketamine, produce psychotomimetic effects in healthy subjects (Krystal et al., 1994) and exacerbate symptoms in patients with schizophrenia (Lahti et al., 1995). Acute administration of ketamine and PCP increases striatal DA levels in rats (Deutch et al., 1987; Moghaddam et al., 1997) and healthy human subjects (Kegeles et al., 2000; Vollenweider et al., 2000). In contrast, chronic administration of an NMDA receptor antagonist has been shown to have no effect on striatal DA levels (Lannes et al., 1991). Amphetamine has also been examined as a schizophrenia model based on clinical evidence that acute administration can increase DA efflux and exacerbate symptoms in patients (Snyder, 1973; Robinson and Becker, 1986). Prolonged amphetamine use in the normal population can lead to paranoid psychosis, but by the time an individual is addicted to amphetamine, the drug elicits a relatively small DA release compared to the initial dose (Castner and Williams, 2007; Nutt et al., 2015). Both NMDA receptor antagonists and amphetamine demonstrate significant differences between their acute and chronic effects that impact the interpretations that can be drawn from their use in animal models.

Pharmacological models are useful for studying the consequences of a manipulation that may have relevance to schizophrenia, but they provide limited value in understanding the etiology of the disease, which must be considered in the discovery of novel APDs. For example, the ability of NMDA receptor antagonists to mimic psychosis does not necessarily mean that NMDA receptors are impaired in schizophrenia, but they have provided insight into pyramidal neuron disinhibition relevant to the glutamatergic dysfunction observed in schizophrenia (Homayoun and Moghaddam, 2007; O'Donnell, 2013). However, the circuit and system-level abnormalities that underlie psychotic symptoms develop over a lifetime in response to genetic and environmental factors (Lewis and Levitt, 2002).

2.2.2. Neurodevelopmental models of schizophrenia—Neurodevelopmental animal models are based on the hypothesis that deviations from normal maturation can

produce long-term changes in the brain. The structural and functional abnormalities that result from early-life insults often only fully emerge in adulthood. This makes developmental models valuable for identifying processes through which a triggering event can progress into a pathological state and evaluating preventative interventions with potential use in the prodromal stage (Meyer and Feldon, 2010).

Developmental consequences are commonly observed from environmental manipulations that involve early-life stress, such as social isolation or maternal separation (Harlow et al., 1965; Meaney et al., 1996). Adversity during the juvenile and adolescent period can shape the maturation of circuits that underlie emotional function (Cohen et al., 2013) and the resulting hyperresponsivity to stress is a core component of many psychiatric disorders (Heim and Nemeroff, 2001; Lupien et al., 2009). A large body of work highlights the importance of stress as a risk factor in the development of schizophrenia (Corcoran et al., 2003; van Os et al., 2010; Holtzman et al., 2013; Gomes and Grace, 2017). The correlation between early life stress and severity of positive symptoms (Ruby et al., 2017) may partially be due to the interaction between stress and the DA system (Belujon and Grace, 2015; Howes et al., 2017). Both UHR individuals and schizophrenia patients demonstrate elevated DA release in response to stress compared to healthy controls (Pruessner et al., 2004; Mizrahi et al., 2012). Furthermore, peripubertal stress exposure in rats has been shown to increase DA neuron activity in adulthood, suggesting that stress before or during puberty is particularly impactful to the responsivity of the DA system (Gomes and Grace, 2016).

The neonatal ventral hippocampal lesion (NVHL) model was the first to test the hypothesis that altered development of the ventral hippocampus (vHPC), a critical site of pathology in schizophrenia, can mimic the developmental course of schizophrenia. The model showed that a vHPC lesion in the early postnatal period results in the adult onset of behavioral abnormalities and DA dysfunction relevant to schizophrenia (Lipska et al., 1992; Lipska and Weinberger, 2000). Inspired by findings from the NVHL model and studies demonstrating the importance of immune activation during pregnancy as a risk factor for schizophrenia (Zuckerman et al., 2003; Canetta and Brown, 2012), another prominent neurodevelopmental model of schizophrenia was developed, the methylazoxymethanol acetate (MAM) model (Johnston et al., 1981; Moore et al., 2006). The MAM model involves administration of the mitotoxin MAM to pregnant dams on gestational day 17, which correlates with the vulnerable timepoint of the 2nd trimester in humans to adverse events such as maternal infection (Brown, 2006). The offspring of MAM-treated dams (“MAM rats”) develop region-specific disruption of neuronal maturation that results in adult phenotypes relevant to schizophrenia, compared to the offspring of dams that receive a saline injection, (“SAL rats”) (Flagstad et al., 2004; Moore et al., 2006; Modinos et al., 2015). Despite their different approaches, both the NVHL model and the MAM model display enhanced responsivity to stress (Lipska et al., 1993; Zimmerman et al., 2013) in addition to similar structural and functional abnormalities in adulthood.

One of the characteristic phenotypes observed in MAM rats is a hyperdopaminergic system. MAM rats demonstrate an increased number of spontaneously active DA neurons in the VTA, referred to as population activity, consistent with the hyperactive presynaptic DA function observed in schizophrenia (Laruelle and Abi-Dargham, 1999; Lodge and Grace,

2007; Howes et al., 2011a). Spontaneously active DA neurons fire in a tonic, irregular pattern in their basal state. When exposed to a behaviorally salient signal, DA neurons respond by firing bursts of action potentials, resulting in phasic DA release. However, only spontaneously active DA neurons can produce burst firing in response to glutamatergic afferents acting on NMDA receptors (Grace and Bunney, 1984; Legault and Wise, 1999; Floresco et al., 2003; Lodge and Grace, 2006b). Regulatory inputs to the VTA normally modulate DA neuron population activity to vary the phasic signal based on environmental context, such as situations that are threatening or rewarding (Floresco et al., 2003; Grace et al., 2007). We propose that pathologically increased DA neuron population activity observed in MAM rats causes stimuli to produce a maximal DA response independent of context (Fig. 1; Lodge and Grace, 2011; Grace and Gomes, 2018), consistent with the “aberrant salience” framework of psychosis (Kapur, 2003). We also propose that the MAM rats are not necessarily “doomed from the womb”, but instead fit a “two hit model” where the early disruption in brain development leads to heightened vulnerability to stress, with the potential for intervention prior to the second hit (Gomes et al., 2016).

2.3. Using the MAM model to study hippocampal drive of DA pathology

The vHPC, the rodent analog of the anterior HPC in humans (Grace, 2016; Heilbronner et al., 2016), plays a critical role in the pathophysiology of schizophrenia. Its involvement in context-based control of DA neuron activity is thought to contribute to the aberrant salience proposed to underlie psychosis (Kapur, 2003; Lisman et al., 2008). Deficits in the structure and function of the HPC are consistently observed in imaging and post-mortem studies of schizophrenia patients (Tamminga et al., 2010). Patients exhibit difficulty recruiting the HPC during tasks (Heckers et al., 1998; Weiss et al., 2003) and increased HPC activity at rest and during cognitive tasks involving processing of salient information (Medoff et al., 2001; Holt et al., 2006; Tregellas et al., 2014). Most studies report increased HPC glutamate levels in both first-episode and chronic patients, independent of medication status (Poels et al., 2014). HPC activity is also linked to disease progression; increased cerebral blood volume (CBV) has been reported in the anterior HPC during the prodromal stage and predicts conversion to psychosis (Harrison, 2004; Schobel et al., 2009) and atrophy of the anterior HPC (Schobel et al., 2013). Cross-sectional comparison of UHR subjects to healthy controls generally does not reveal differences in HPC volume between the two populations (Velakoulis et al., 2006; Wood et al., 2008). However, longitudinal studies have demonstrated that UHR patients that convert to psychosis show a greater progression of grey matter reduction of the anterior CA1 and subiculum compared to those who do not convert to psychosis (Pantelis et al., 2003; Borgwardt et al., 2007; Schobel et al., 2013). Reduced volume of the anterior HPC has also been associated with illness duration (Velakoulis et al., 2006), although not all studies have found significant reduction over time (Lieberman et al., 2001) and chronic APD treatment or other external factors may contribute to progressive volume loss (Ho et al., 2011; Zipursky et al., 2012). Excitotoxicity from sustained oxidative stress may explain the correlation between increased regional glutamate levels and corresponding reduction in volume found in neuroimaging studies (Benes, 2000; Kraguljac et al., 2013; Do et al., 2015). Together, these findings suggest a strong link between HPC pathology and the onset of psychosis.

The MAM model has provided critical insights into how HPC pathology leads to increased DA neuron activity (Fig. 1). Silent DA neurons are held in a hyperpolarized state by the ventral pallidum, which is controlled by a circuit originating with the vHPC (Floresco et al., 2001; Lodge and Grace, 2006b). Both schizophrenia patients (Benes and Berretta, 2001) and MAM rats (Gill and Grace, 2014) show loss of parvalbumin (PV+) interneurons in the vHPC that provide inhibitory control of pyramidal cell activity, resulting in a baseline hyperactive state. Increased vHPC drive indirectly releases DA neurons from inhibition, which increases the population of spontaneously active DA neurons available for phasic burst firing in response to glutamatergic input from the pedunculopontine tegmentum (PPTg) (Floresco et al., 2001), which itself is enabled by the laterodorsal tegmentum (LDT) (Lodge and Grace, 2006a). Activation of the vHPC in normal rats dramatically increases DA neuron population activity in the VTA that is correlated with increased DA efflux in the associative areas of the ventral striatum and NAc, whereas inactivation of vHPC in MAM rats can normalize the DA neuron activity and related aberrant behavior (Floresco et al., 2003; Lodge and Grace, 2007). Current APDs reduce DA neuron hyperactivity through their action on D₂ receptors, but they do not target or resolve the HPC pathology, instead working as many as 5 synapses downstream from the apparent site of pathology.

3. Antipsychotic drug regulation of dopamine system dysfunction

3.1. D₂ receptor antagonists

Much of the research on APDs has focused on their mechanisms of action to understand how they achieve their therapeutic effect. APDs are traditionally categorized as either first-generation antipsychotics (FGAs), such as haloperidol, or second-generation antipsychotics (SGAs), such as clozapine, which act on a larger spectrum of receptor types, including serotonergic, cholinergic, and adrenergic receptors (Miyamoto et al., 2005). Due to the high level of heterogeneity within these broad designations, some argue that the current nomenclature is uninformative and should be replaced with a neuroscience-based naming system (Zohar et al., 2015). Like many psychoactive drugs, APDs have numerous physiological effects due to their rich pharmacology, although the antipsychotic effect of both FGAs and SGAs remains dependent on the D₂ receptor and are given at doses that match D₂ occupancy (Kapur and Remington, 2001). Most current APDs act as D₂ receptor antagonists (Seeman, 1987), but to understand how FGAs and SGAs regulate the DA system, it is necessary to look beyond the receptor at downstream consequences on DA neuron activity.

D₂ antagonists block both postsynaptic and presynaptic D₂ receptors. Acute administration of D₂ antagonists in anesthetized rats increases DA neuron firing rate and bursting activity, primarily through blockade of somatodendritic D₂ autoreceptors that normally provide negative feedback for the neuron (Grace and Bunney, 1986; Pucak and Grace, 1994). However, with repeated treatment there is a substantially depolarized membrane potential that culminates in inactivation such that the DA neuron is no longer able to generate action potentials. The inactivation can be reversed by compounds that inhibit DA neurons, such as DA agonists, whereas excitatory compounds are no longer capable of stimulating activity (White and Wang, 1983; Grace and Bunney, 1986). This phenomenon, referred to as

depolarization block, is proposed to underlie the regulatory action of D₂ antagonists on DA neuron hyperactivity (Fig. 2A). This review will discuss some of the consequences of depolarization block, but for more detailed reviews on APD regulation of the DA system see (Grace et al., 1997; Arnt and Skarsfeldt, 1998).

FGAs and SGAs have similar efficacy on positive symptoms and they are primarily distinguished in clinical use by differing side effect profiles (Leucht et al., 2013). One hypothesis is that APD efficacy is related to inhibition of DA function in the VTA, whereas extrapyramidal symptoms (EPS) are mediated by inhibition of DA function in the substantia nigra (SNc) (Deutch et al., 1991). Therefore, differences in specificity of depolarization block between FGAs and SGAs may explain their comparable efficacy and difference in propensity to cause EPS (Fig. 2; Haro and Salvador-Carulla, 2006; Correll and Schenk, 2008). Acute administration of FGAs activates DA neurons in both the VTA and substantia nigra (SNc), whereas SGAs only activate DA neurons in the VTA (Bunney and Grace, 1978; Chiodo and Bunney, 1985; Goldstein et al., 1993; Stockton and Rasmussen, 1996). Accordingly, FGAs produce depolarization block in both the VTA and SNc, whereas SGAs selectively produce depolarization block in the VTA (Chiodo and Bunney, 1983; White and Wang, 1983; Grace and Bunney, 1986; Lane and Blaha, 1987; Goldstein et al., 1993). It has been suggested that differing pharmacokinetics may also contribute to their side effect profiles: SGAs typically dissociate from the D₂ receptor more readily than FGAs, which may make them more accommodating to physiological DA transmission (Kapur and Seeman, 2001). In support of this hypothesis, quetiapine and clozapine, the SGAs with the fastest dissociation rates, show no greater risk of EPS than placebo across their dosage range, whereas risperidone and olanzapine, SGAs with slower dissociation rates from the D₂ receptor, are more likely to cause EPS at high doses (Kapur and Seeman, 2001). Of course, this depends on how EPS are defined. Whereas the FGAs cause motor-related EPS like Parkinson's symptoms and tardive dyskinesia, akathisia is a dose-dependent adverse effect of all APDs, including SGAs and some D₂ partial agonists (Berman et al., 2007; Kane et al., 2009). Although akathisia was initially classified as EPS, the fact that the motor activation is driven more by agitation or anxiety suggest a limbic origin of this symptom.

The onset of depolarization block may relate to the range of latencies in clinical improvement of psychosis, which can occur as fast as 24 h following the initial dose of an APD, with full effect after several weeks of treatment (Agid et al., 2003; Kapur et al., 2005; Leucht et al., 2005). In normal rats, 21 d repeated administration of FGAs and SGAs is necessary to reduce the number of spontaneously active DA neurons (Chiodo and Bunney, 1983; Grace and Bunney, 1986), whereas MAM rats undergo rapid onset of depolarization block following acute administration (Valenti et al., 2011). Enhanced DA system excitability in MAM rats likely underlies the rapid onset of depolarization block. This is consistent with clinical studies showing that patients with the highest level of psychosis, implicating a more hyperactive DA system, tend to show a rapid response to APD treatment (Robinson et al., 1999).

Depolarization block has been observed across numerous studies in rats, but questions remain about the consistency and consequences of the phenomenon. Some have argued that it may be an artifact of anesthesia (Mereu et al., 1995; Melis et al., 1998). However, chloral

hydrate, the anesthesia used for DA neuron recordings, normally blunts the excitatory response of DA neurons to APDs (Bunney et al., 1973) and depolarization block has been observed in nonanesthetized, paralyzed rats (Bunney and Grace, 1978; Chiodo and Bunney, 1985). There have also been inconsistencies on the effect of depolarization block on striatal DA release. Some have reported a reduction in basal DA release that corresponds with depolarization block (Blaha and Lane, 1987; Lane and Blaha, 1987; Moore et al., 1998), whereas others have not found a difference in striatal DA levels (Ichikawa and Meltzer, 1991; Moghaddam and Bunney, 1993). However, the lesion produced from microdialysis probe insertion was later found to disrupt depolarization block, and the issue can be avoided by implanting the microdialysis probe prior to APD administration (Moore et al., 1998). The long-term changes to DA neuron activity following APD withdrawal are also unclear and require further investigation. We previously found that DA neuron activity remains reduced for at least a week following repeated D₂ antagonist administration in both MAM and SAL rats (Gill et al., 2014). However, population activity is no longer restored with administration of a DA agonist, indicating that the reduction following withdrawal may no longer be caused by depolarization block and may be due to other compensatory mechanisms (Gill et al., 2014).

It has long been suggested that neuroadaptations to chronically administered psychiatric drugs can produce discontinuation syndromes and facilitate relapse, with rapid withdrawal inducing greater relapse (Viguera et al., 1997). One of the consequences of chronic D₂ antagonist treatment is D₂ receptor upregulation (Silvestri et al., 2000; Samaha et al., 2007), which can produce a state referred to as DA supersensitivity (Fig. 2; Chouinard et al., 2017). Development of DA supersensitivity has been attributed to breakthrough symptoms and the rapid rate of relapse following APD discontinuation or dose reduction, which often results in new and more severe symptoms (Chouinard and Jones, 1980; Chouinard et al., 2017). Studies in rats have demonstrated that DA supersensitivity occurs both during and after treatment, potentially accounting for breakthrough symptoms, although the consequences are more apparent following withdrawal (Samaha et al., 2007). Some have argued that breakthrough symptoms are more likely due to treatment noncompliance and can be circumvented by continuous blood levels using long acting injectables (LAIs) (Correll et al., 2018). However, long-term treatment with LAIs has been shown to provide modest, if any, reduction in the rate of relapse compared to oral administration in randomized controlled trials (Kishimoto et al., 2012) and roughly 20% of patients relapse within a year (Leucht et al., 2011). Further research on the interrelated topics of APD tolerance, withdrawal, and relapse is critical for clear guidelines on switching between APDs and determining which patients would benefit from dose reduction following stabilization (Murray et al., 2016). Indeed, one would predict that after the onset of depolarization block, the resultant decrease in DA release would require a lower APD dose to maintain this state. Despite the increase in D₂ receptors, less therapeutic tolerance occurs to APDs in a clinical setting than what would be expected from antagonism of a receptor, which may be due to the indirect method of DA neuron regulation (i.e. depolarization block); however, the reduction of DA neuron activity is far from returning the system to a normal state (Fig. 2B).

3.2. D₂ partial agonists

D₂ partial agonists, such as aripiprazole, activate the receptor to a lower degree than endogenous DA and are sometimes referred to as third generation antipsychotics. They are thought to stabilize DA neurotransmission by reducing excessive striatal D₂ stimulation and restoring deficient D₂ stimulation in regions including the prefrontal cortex (Grace, 1991; Burris et al., 2002). In contrast to D₂ antagonists, which are associated with a therapeutic effect at striatal D₂ receptor occupancy of 65-70% and increased risk of EPS at D₂ receptor occupancy exceeding 80% (Farde et al., 1992; Kapur et al., 2000), aripiprazole has a therapeutic effect with 85-95% striatal D₂ receptor occupation, yet does not produce EPS (Yokoi et al., 2002; Mamo et al., 2007). Furthermore, aripiprazole has been shown to not produce D₂ receptor upregulation or behavioral DA supersensitivity in rats (Fig. 2; Inoue et al., 1997; Tadokoro et al., 2011), and there is preliminary evidence that it may alleviate DA supersensitivity in humans (Tadokoro et al., 2017). D₂ receptor partial agonists may thus be less likely to induce adverse effects related to DA supersensitivity, as observed following chronic D₂ antagonist treatment (Silvestri et al., 2000; Chouinard et al., 2017). These differences between D₂ receptor antagonists and D₂ partial agonists may be related to their distinct methods of DA neuron regulation.

Like the rapid reduction of DA neuron population activity in MAM rats in response to D₂ receptor antagonist administration, acute aripiprazole administration also reduces the number of spontaneously active DA neurons in MAM rats (Valenti et al., 2011; Sonnenschein et al., 2019). The reduction in DA neuron activity in MAM rats remains stabilized following 1-week withdrawal from repeated aripiprazole administration, as previously observed following withdrawal from repeated haloperidol treatment (Gill et al., 2014; Sonnenschein et al., 2019). However, unlike D₂ receptor antagonists (Valenti et al., 2011; Gill et al., 2014), neither acute nor repeated aripiprazole administration shows an effect on DA neuron population activity in normal rats (Sonnenschein et al., 2019). This is consistent with studies showing, in contrast to MAM rats, no effect of acute or repeated D₂ partial agonist p.o. administration on extracellular DA levels in normal rats across a range of dosages (Jordan et al., 2004; Maeda et al., 2014) and suggests distinct functional effects dependent on the state of the DA system, in line with its action as a partial agonist. Other studies, using i.p. administration, have reported regional, dose dependent changes in DA levels in response to aripiprazole, which may relate to the different administration method (Li et al., 2004).

Despite aripiprazole's antagonist-like reduction of hyperdopaminergic activity in MAM rats, it does not act via depolarization block (Fig. 2). Low doses of apomorphine either failed to restore, or further reduced, DA neuron population activity in MAM rats (Sonnenschein et al., 2019). No significant differences were observed in average firing rate and bursting activity across the total population of DA neurons recorded between aripiprazole and vehicle-treated MAM rats, p.o. (Sonnenschein et al., 2019), but acute i.p. aripiprazole administration has been shown to reduce DA neuron firing rate and bursting activity (Bortolozzi et al., 2007; Dahan et al., 2009; Sonnenschein et al., 2019), suggesting that it may reduce DA neuron population activity through action on presynaptic D₂ receptors to downregulate DA neuron activity (Fig. 3). The greater number of presynaptic spare receptors may underlie

aripiprazole's agonist-like action on D₂ autoreceptors to inhibit DA neuron activity (Kikuchi et al., 1995; Burris et al., 2002), while its lower intrinsic activity at the receptor than a full agonist may simultaneously explain its antagonist-like effect at postsynaptic D₂ receptors in states of DA hyperactivity, such as blockade of apomorphine-induced hyperlocomotion and stereotypy (Kikuchi et al., 1995). Indeed, aripiprazole has been shown to reverse depolarization block in haloperidol-treated MAM rats (Sonnenschein et al., 2019), resembling depolarization block reversal following low-dose DA agonist administration (Valenti et al., 2011). This phenomenon may relate to the temporary worsening of psychotic symptoms reported in patients transitioning to aripiprazole from D₂ antagonist treatment (Takase et al., 2015; Tadokoro et al., 2017).

It is difficult to conclude whether receptor reserve entirely accounts for aripiprazole's complex effects across a range of systems. It has been suggested from *in vitro* studies that aripiprazole possesses functional selectivity dependent on the cellular environment of the receptor and the G protein-coupled receptor (GPCR) signaling pathway activated, which may contribute to its state-dependent effects (Lawler et al., 1999; Shapiro et al., 2003; Mailman and Gay, 2004; Urban et al., 2007). Aripiprazole may lack biased signaling *in vivo*, but it has served as a template for β -arrestin-biased D₂ receptor ligands that have recently been studied as potential APD compounds to more effectively target both cortical and striatal DA dysfunction (Urs et al., 2017). Additional *in vivo* studies are needed to determine the mechanisms underlying aripiprazole's selective downregulation of DA neuron activity in MAM rats and whether they can be generalized to all D₂ receptor partial agonists.

4. Use of animal models in predicting efficacy of novel compounds

4.1. The necessity of novel antipsychotic mechanisms

A key goal of APD research is the development of personalized medication, which requires reliable biomarkers to determine which treatment is most suitable for a patient's individual needs. Approximately 20-30% of patients with schizophrenia display treatment resistance with little or no response to standard medication (Conley and Buchanan, 1997) and a higher rate, up to 60%, only partially respond to treatment (Kane, 1989). Even clozapine, the treatment of choice for refractory symptoms, can be ineffective in approximately 40-70% of patients who take it (Kane et al., 1988; Meltzer et al., 1989; Lieberman et al., 1994; Remington et al., 2005). In the event of inadequate response, clinicians often resort to the combination of multiple APDs, with a wide range of approximately 10-50% of patients treated by polypharmacy, depending on the clinical setting (Stahl and Grady, 2004; Faries et al., 2005; Fleischhacker and Uchida, 2014). Despite its prevalence, there is limited evidence that long-term APD polypharmacy benefits patients (Stahl and Grady, 2004), and may instead be detrimental due to increased frequency of adverse effects (Correll et al., 2007; De Hert et al., 2012).

Treatment resistance can occur in patients who once responded to APDs but no longer do, which can occur following relapse and may be related to DA supersensitivity (Emsley et al., 2013). There are also patients who never responded to APDs whose psychotic symptoms have been proposed to not involve DA dysregulation (Howes and Kapur, 2014). Studies have shown that schizophrenia patients with low striatal DA synthesis capacity, and thus fewer

DA neurons active, are more likely to be treatment non-responders (Demjaha et al., 2012; Demjaha et al., 2014). Given that a more active DA system responds faster to D₂ blockade, this subset of patients may still have a pathology involving the DA system, but the low responsivity of their DA system would not be a pathology conducive to induction of depolarization block or other means of DA neuron downregulation (Grace and Gomes, 2018). However, these patients still show signs of glutamatergic dysfunction, including higher glutamate levels in the anterior cingulate compared to treatment responders (Demjaha et al., 2014), suggesting that targeting the glutamatergic pathology may alleviate symptoms for both treatment responders and non-responders. Current APDs exclusively target the DA system, necessitating further development of novel target options for treatment resistant patients.

Among both treatment responders and nonresponders, there remain unmet needs in tolerability and safety of current APDs. In recent years, concern has been raised about the risk-to-benefit ratio of maintenance APD treatment, due to issues including DA supersensitivity and potential deleterious effects on brain structure and functioning (Murray et al., 2016; Chouinard et al., 2017). Treating patients with the minimum necessary dose and using D₂ partial agonists may minimize side effects and the risks associated with long term APD treatment, but treating the disease closer to the site of pathology may circumvent the issues associated with D₂-targeting drugs and address additional symptoms. To improve functional outcome, an ideal treatment would also address negative symptoms and cognitive deficits (Green et al., 2000; Milev et al., 2005), but this may be more readily accomplished through the use of adjunctive treatments that are not necessarily disease specific (Carpenter and Koenig, 2008). However, given that the vHPC is dysrhythmic and hyperactive, and projects not only to the DA controlling regions but also to the prefrontal cortex and amygdala, normalizing vHPC activity may provide symptomatic relief across all symptom classes (Fig. 3; Grace and Gomes, 2018).

4.2. The rise and fall of novel target compounds

A massive investment has gone into the development of novel target compounds with the hope that they would be more effective in treating the positive symptoms of schizophrenia, in addition to negative and cognitive symptoms. A common theme among them was promising performance in preclinical research, but failure to show sufficient antipsychotic efficacy in larger clinical trials (Dunlop and Brandon, 2015). However, a common caveat is that in preclinical trials, all drugs were tested on APD-naïve animals, whereas in clinical trials the drugs were all tested on schizophrenia patients that had received long courses of APD therapy. This review focuses on two of the novel target compounds that were aimed at regulating glutamatergic abnormalities in schizophrenia.

4.2.1 Glycine Transport Inhibitors—A number of potential APD compounds were developed based on findings that NMDA receptor antagonists can produce effects similar to the symptoms of schizophrenia. Blockade of NMDA receptors on PV+ interneurons results in disinhibition of pyramidal cell activity similar to the dysregulated pyramidal cell activity observed in schizophrenia (Homayoun and Moghaddam, 2007; Schobel et al., 2013), which led to efforts to enhance NMDA receptor function in patients (Coyle et al., 2003). Both

glutamate and glycine sites need to be occupied on NMDA receptors for the channel to open, but direct drug action at the glutamate site can be toxic (Thomson et al., 1989). There was initial promise in initial clinical studies using glycine or D-serine, the endogenous co-agonist of NMDA receptors (Mothet et al., 2000), as an adjunct to existing APDs to improve positive, negative, and cognitive symptoms in schizophrenia (Heresco-Levy et al., 1996; Tsai et al., 1998; Heresco-Levy et al., 1999; Evins et al., 2000; Javitt et al., 2001; Evins et al., 2002; Heresco-Levy et al., 2002; Heresco-Levy et al., 2004; Heresco-Levy et al., 2005), though larger, longer studies did not yield positive results (Goff et al., 2005; Buchanan et al., 2007; Weiser et al., 2012). A selective glycine transporter 1 (GlyT1) inhibitor was studied as an alternative strategy with greater brain penetrance to increase the availability of glycine to bind to NMDA receptors (Javitt, 2012). The most extensively studied GlyT1 inhibitor was bitopertin from Roche. Bitopertin showed promise in preclinical research, including reversing amphetamine-induced hyperlocomotion in both naïve mice and mice chronically treated with PCP (Alberati et al., 2012). Despite some initial success of a similar compound as an adjunct therapy (Tsai et al., 2004), biopertin failed to demonstrate efficacy in both phase 2 clinical trials (Umbricht et al., 2014) and phase 3 clinical trials as either a monotherapy or adjunct therapy compared to standard treatment (Bugarski-Kirola et al., 2014; Bugarski-Kirola et al., 2016; Bugarski-Kirola et al., 2017). Biopertin was grounded in decades of research on the potential of targeting glutamatergic dysfunction, yet, like other novel target compounds tested at the time, followed the trend of initial success leading to failure to replicate in larger clinical trials, potentially due to patient heterogeneity (Goff, 2014).

4.2.2. mGluR2/3 agonists—Group II metabotropic glutamate receptor (mGluR2/3) agonists were another promising novel target compound investigated for the treatment of schizophrenia. They were designed to regulate glutamate release by acting on the presynaptic mGluR2/3 receptors located on glutamatergic terminals in cortical and limbic brain regions (Nicoletti et al., 2011). Following extensive preclinical support for mGluR2/3 as an APD target (Moghaddam and Adams, 1998; Cartmell et al., 1999, 2000; Lorrain et al., 2003; Greenslade and Mitchell, 2004; Homayoun et al., 2005; Pehrson and Moghaddam, 2010), an mGluR2/3 agonist from Eli Lilly, pomaglumetad methionil, was advanced to clinical trials. It showed promise in preclinical research, including reversing effects caused by NMDA receptor antagonists, blocking amphetamine-induced hyperlocomotion, and showing anxiolytic effects in models of anxiety (Rorick-Kehn et al., 2007; Mezler et al., 2010). It demonstrated potential as a monotherapy in its first double-blind, randomized, placebo-controlled phase 2 clinical trial, and it was found to be well tolerated with no propensity to cause weight gain or EPS (Patil et al., 2007). This success was followed by a long line of disappointments in subsequent phase 2 trials as a monotherapy or adjunct therapy (Adams et al., 2013; Stauffer et al., 2013; Downing et al., 2014) and failure to meet the primary endpoint as a monotherapy in a large phase 3 trial (Adams et al., 2014; J Marek, 2015). Later analyses of the clinical trials found that certain populations responded better to pomaglumetad (Kinon et al., 2015), leaving questions about why those groups responded better and whether glutamatergic-targeting therapies may be best suited for certain populations. For example, early-in-disease patients responded better to pomaglumetad treatment than chronic patients (Kinon et al., 2015), which could potentially be due to

factors including treatment history and disease progression. Additionally, a study in mice showed that SGA administration can downregulate mGluR2 expression, thought to be due to action on 5-HT_{2A} receptors, which may have contributed to the failure (Kurita et al., 2012). There were also efforts to develop mGluR2 positive allosteric modulators (PAMs) that would induce a leftward shift in the dose-response curve for glutamate without directly acting at the glutamate site (Conn et al., 2009; Fraley, 2009; Fell et al., 2012). They similarly showed promising results in APD screening assays (Lavreysen et al., 2013), though a compound tested by AstraZeneca once again did not show efficacy in patients with schizophrenia as a monotherapy (Litman et al., 2016). Despite the failure of the clinical trials, they are suggestive that there may be sub-populations of patients who may benefit most from novel drugs and they also highlight the need to study the effects of prior APD treatment.

4.3 Future directions in preclinical research for novel target antipsychotic drugs

The mechanisms of action tested in clinical trials were derived from decades of human and animal model research showing excitatory-inhibitory imbalance as a core component of schizophrenia and a promising target across symptom domains. Their failure created uncertainty in the current theoretical framework of schizophrenia regarding the potential to treat glutamatergic dysfunction. Moving forward, one option is to leave these mechanisms of action in the “pharmaceutical graveyard” and forgo pursuit of similar novel target compounds for the treatment of schizophrenia. Alternatively, we propose that these drugs, or others based on similar theoretical concepts, still hold promise, but require additional preclinical screening to better conduct clinical trials. A particular caveat is that the prior clinical trial protocol was based on finding more effective D₂ antagonist APDs, such that switching from one D₂ antagonist to another may not be as critical an issue. However, when testing novel target compounds, prior treatment history may significantly impact the results.

4.3.1. Animal Model Selection and Interpretation—The brain of a patient with schizophrenia who has had years of APD exposure is distinct from that of a drug naïve patient or a healthy volunteer. Consequently, normal animals are useful as a blank slate to examine the effects of a drug, but they are not well-suited for APD screening compared to approaches that incorporate disease-relevant abnormalities. For example, D₂ antagonists and D₂ partial agonists function differently in a hyperdopaminergic state, as observed in the MAM model of schizophrenia, which may be more representative of how they act in a patient (Valenti et al., 2011; Sonnenschein et al., 2019). The choice of proper animal models and assays to study APDs is particularly important when testing novel mechanisms.

There has been much debate over whether current preclinical assays of APD efficacy are useful for screening novel mechanisms of action (Carpenter and Koenig, 2008; Nestler and Hyman, 2010). For example, blockade of amphetamine-induced hyperlocomotion is a behavioral task in rodents commonly used to predict APD efficacy to treat positive symptoms. However, amphetamine-induced hyperlocomotion is believed to arise from a ventromedial limbic striatal action (Creese and Iversen, 1975), whereas imaging studies show that increased raclopride displacement and increased f-DOPA uptake that correlate with psychosis is present primarily in the associative striatum (Kegeles et al., 2010; Kesby et

al., 2018). Hypodopaminergic signaling has been observed in extra-striatal regions, and DA deficits in the dorsolateral prefrontal cortex in particular is thought to contribute to cognitive deficits in schizophrenia (Slifstein et al., 2015). It is currently unknown what accounts for these coexisting differences in DA regulation, which have yet to be demonstrated in an animal model. Given the current models available, a more effective screen should selectively target DA release in the associative striatum, such as a task that addresses the role of DA function in salience attribution and selective attention, which may be a more reliable measure of APD efficacy. Additionally, behavioral tasks that do not result in obvious face validity should not be considered irrelevant to the disease, as common neurobiological effects could underlie different behavioral phenotypes across species.

Drug dosage and administration methods are critical factors in demonstrating consistent effects, both when comparing between animal studies and translating between animal and human research. Metabolic differences must be considered to determine corresponding receptor occupancy (Kapur et al., 2003) in addition to the administration method, particularly when looking at the effects of repeated treatment. Transient APD delivery was found to be more effective than continuous D₂ blockade, which was more likely to result in D₂ receptor upregulation and behavioral tolerance. It has been reported that continuous administration may be more likely to result in DA supersensitivity (Samaha et al., 2008), whereas intermittent dosing with “drug holidays” is more likely to maintain efficacy (Remington and Kapur, 2010). Given that patients typically receive long-term APD treatment, animal research would benefit from implementing more chronic treatment studies to examine long-term responses and identify any compensatory mechanisms, including changes in receptor response and more widescale changes in circuit plasticity.

4.3.2. Treatment History—Preclinical modeling can be used to determine the contribution of chronic APD treatment in clinical findings. We previously found that 1 week withdrawal from repeated haloperidol treatment produces persistent DA supersensitivity in MAM rats, interfering with the ability of a novel target compound to reduce amphetamine-induced hyperlocomotion, in contrast to its ability to regulate DA hyperresponsivity in drug-naïve rats (Gill et al., 2011; Gill et al., 2014). While the washout period of 1-2 weeks typically used in clinical studies may be adequate to decrease blood levels of the APD, the study demonstrates that a short withdrawal period is not sufficient to reverse the effects of the drug on the DA system. It also raises the possibility that DA supersensitivity following prior D₂ antagonist treatment in patients with schizophrenia may similarly mask potential effects of novel target compounds in clinical trials, despite their promise in screening assays performed in normal, drug-naïve rodents. The results of the trial could potentially be confounded by the long-lasting changes in the system made by the presence of the APD, which may contribute to why the novel drugs performed better in early-in-disease patients (Kinon et al., 2015). In the presence of D₂ receptor upregulation following chronic D₂ receptor antagonist treatment (Silvestri et al., 2000; Samaha et al., 2007), it is possible that only another D₂ receptor-targeting drug may be effective in reversing hyperresponsivity to DA.

4.3.3. Targeting Upstream Pathology—Future development of APDs should aim to provide normal regulation of DA neuron activity rather than general suppression of DA neurotransmission. Given the large amount of evidence that loss of PV+ interneuron regulation of pyramidal cell activity underlies many aspects of schizophrenia, including its role in DA system hyperactivity, it still holds promise as an APD target and may avoid consequences associated with D₂ antagonist treatment. Targeting excitatory-inhibitory processes may also alleviate more symptoms of the disorder, including negative and cognitive symptoms, which often precede the first psychotic episode and persist after treatment of psychotic symptoms (Harvey et al., 2005). Several studies from our lab and others have found success with using strategies to target vHPC dysfunction to normalize DA neuron activity and behavior in MAM rats (Gill et al., 2011; Gastambide et al., 2012; Perez and Lodge, 2013; Perez et al., 2013).

Targeting upstream pathology has the potential to be more effective in treating schizophrenia in patients who have already developed the disease, but an ideal approach would involve intervention prior to the transition to psychosis, which may lead to a better long-term outcome (Perkins et al., 2005; Gomes et al., 2016; Grace and Gomes, 2018). Treatment of glutamatergic dysfunction during the pre or peri-pubertal period can produce long-lasting effects on DA function based on studies in MAM rats. Prior to puberty, rats do not display the full expression of MAM-associated phenotypes (Moore et al., 2006). Peripubertal administration of the benzodiazepine diazepam has been shown to attenuate the increased anxiety-like behavior and basolateral amygdala hyperactivity normally present in MAM rats. The reduced stress response also likely underlies the decreased PV+ interneuron loss in the vHPC and prevention of hyperdopaminergic activity in adult MAM rats observed following peripubertal diazepam administration (Du and Grace, 2013, 2016b, a). Benzodiazepines are not a realistic prophylactic option clinically due to a number of issues including dependence and tolerance, but it demonstrates the potential long-term benefits of treatment during the peripubertal period. It has been reported that increased HPC activity, local reduction in PV+ interneurons, and volume loss following repeated ketamine administration in mice can be prevented by coadministration with an mGluR2/3 agonist. However, the same drug may lose its efficacy for patients with long-standing illness (Kinon et al., 2015). Together, these studies suggest that decreasing stress or other means of reducing HPC activity prior to the first episode (Schobel et al., 2013) could circumvent the damage that leads to the emergence of the DA dysregulation and psychotic symptoms (Gomes et al., 2016; Grace and Gomes, 2018). They also suggest the potential for stage-specific pharmacotherapies whereby patients may have options for optimal treatment strategies based on the neurobiological course of the disease (Krystal and Anticevic, 2015).

5. Conclusion

Animal research has provided critical insight into the mechanisms of action of current APDs and a framework to test hypotheses about the neurobiology underlying schizophrenia. The failure of recent novel target drugs does not invalidate the theory behind their development, but highlights the gaps that exist in their translation. In particular, studies performed in the MAM model have demonstrated the importance of studying the effects of APDs on a system representative of patients. Their hyperdopaminergic pathology shows rapid onset of

depolarization block to D₂ antagonists and responds to D₂ partial agonists through a manner distinct from depolarization block (Valenti et al., 2011; Sonnenschein et al., 2019). These findings are consistent with clinical results and not observed in normal rats. We also propose that therapeutic strategies should be directed on upstream factors that control presynaptic release of DA. However, the effects of prior APD treatment must be considered in the development of novel drugs. Most patients receive chronic treatment with APDs, resulting in long-lasting changes to the brain that are not represented in normal or drug-naïve rats. Results from the MAM model have suggested that this may be a significant factor in novel-target response, which was prevented due to persistent DA supersensitivity from prior D₂ antagonist treatment (Gill et al., 2014). In contrast, evidence suggests that the partial agonist aripiprazole does not induce DA supersensitivity (Tadokoro et al., 2011). Thus, testing novel compounds on patients who are withdrawn from aripiprazole, drug-naïve, or confirmed to be non-compliant with their prior medication may be more effective strategies. Additionally, it is important to determine whether novel target compounds are effective in patients that are treatment resistant to current APDs. The MAM model also has shown that pharmacological methods can be used to prevent full emergence the pathology in adulthood (Du and Grace, 2013, 2016b, a). These findings suggest the potential of targeting glutamatergic dysfunction early in the disease to alleviate symptoms and potentially prevent conversion of psychosis. Animal models are best applied in collaboration with studies performed in patients to find parallels and test predictions. Representative animal models, informed by clinical studies, can then be used to investigate the contribution of variables that underlie patient heterogeneity. These findings must then be incorporated into the design of clinical trials of novel target compounds, or else promising targets may be abandoned despite great potential to improve treatment options for schizophrenia.

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- Failure of recent novel target antipsychotics reveals a critical gap in translational research.
- Antipsychotics can have different effects depending on the state of the dopamine system.
- Representative models may provide better predictive validity than normal rodents.

Figure 1.

Hippocampal-striatal regulation of DA neuron activity in normal and schizophrenia. **A)** In a normal system, the limbic hippocampus (HPC), regulates dopamine (DA) neuron population activity in the ventral tegmental area (VTA), with variable gain based on context. The HPC sends glutamatergic input to the nucleus accumbens in the ventral striatum, which sends inhibitory projections to the ventral pallidum. The ventral pallidum holds a proportion of DA neurons in an inhibited state. In response to relevant stimuli, only spontaneously active DA neurons can respond to glutamatergic input from the pedunculopontine tegmentum (PPTg),

gated by the laterodorsal tegmentum (LDT), with burst firing. The DA signal to the striatum has topographic organization with DA neurons in the substantia nigra pars compacta (SNc) projections to the dorsal striatum, lateral VTA projections to the associative striatum, and medial VTA projections to the ventral striatum. **B)** In schizophrenia, the limbic HPC is in a pathologically hyperactive state and no longer responds appropriately to context. Increased excitatory input from HPC to the ventral striatum results in less inhibition of the ventral pallidum and fewer DA neurons held in a silent state. The increased DA signal is most prevalent in the associative striatum.

Figure 2.

Antipsychotic drug modulation of DA neuron activity states. **A)** First generation D_2 antagonist antipsychotic drugs (APDs) act on postsynaptic and presynaptic D_2 receptors in the striatum to produce depolarization block of DA neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) and reduces DA neuron population activity in both regions. The DA signal is diminished to all domains of the striatum, resulting in both the antipsychotic effect and extrapyramidal side effects, including motor dysfunction. Following prolonged treatment, the system adapts by upregulating the number of D_2

receptors, which can produce DA supersensitivity. **B)** Second generation D₂ antagonist APDs only produce depolarization block of DA neurons in the ventral tegmental area (VTA), resulting in a reduced DA signal to the associative and ventral striatum without effect on the DA neurons that project to the dorsal striatum. Thus, SGAs produce an antipsychotic effect without motor side effects. However, like first generation APDs, following prolonged treatment, there is an upregulation of D₂ receptors, which can produce DA supersensitivity. **C)** D₂ partial agonists normalize DA neuron population activity by reducing hyperdopaminergic activity via DA neuron inhibition and increasing hypodopaminergic activity via postsynaptic stimulation. The downregulation of DA neuron activity does not occur through depolarization block and does not produce an upregulation of D₂ receptors.

Figure 3.

A proposed model for ntipsychotic drug effects on symptom domains of schizophrenia. **A)** In schizophrenia, a hyperactive and dysrhythmic limbic hippocampus (HPC) contributes to positive symptoms through its indirect regulation of DA activity in the ventral tegmental area (VTA), which projects to the associative striatum. It also contributes to negative and cognitive symptoms through its disruption of activity patterns with regions including the prefrontal cortex (PFC) and amygdala. All current antipsychotic drugs (APDs) act on D_2 receptors in the striatum, which results in a reduction in positive symptoms, but produce minimal benefit on cognitive symptoms or negative symptoms. **B)** Compounds that target the site of pathology in the limbic HPC by either increasing function of parvalbumin positive interneurons (PVI) or reducing the activity of pyramidal neurons (Pyr) should normalize

hippocampal output and thereby may be more beneficial in treating all symptom domains of schizophrenia.

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