Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2014 October 3; 0: 83–91. doi:10.1016/j.pnpbp.2014.05.001.

Effects of Antipsychotic D2 Antagonists on Long-Term Potentiation in Animals and Implications for Human Studies

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Abstract

In people with schizophrenia, cognitive abilities - including memory - are strongly associated with functional outcome. Long-term potentiation (LTP) is a form of neuroplasticity that is believed to be the physiological basis for memory. It has been postulated that antipsychotic medication can impair long-term potentiation and cognition by altering dopaminergic transmission. Thus, a systematic review was performed in order to assess the relationship between antipsychotics and D2 antagonists on long-term potentiation.

The majority of studies on LTP and antipsychotics have found that acute administration of antipsychotics was associated with impairments in LTP in wild type animals. In contrast, chronic administration and acute antipsychotics in animal models of schizophrenia were not. Typical and atypical antipsychotics and other D2 antagonists behaved similarly, with the exception of clozapine and olanzapine. Clozapine caused potentiation independent of tetanization, while olanzapine facilitated tetanus-induced potentiation.

These studies are limited in their ability to model the effects of antipsychotics in patients with schizophrenia as they were largely performed in wild type animals as opposed to humans with schizophrenia, and assessed after acute rather than chronic treatment. Further studies using patients with schizophrenia receiving chronic antipsychotic treatment are needed to better understand the effects of these medications in this population.

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Keywords

animals; antipsychotics; D2; humans; LTP; neurophysiology

Long-term potentiation (LTP) is a form of neuroplasticity that is believed to be the physiological basis for memory. In people with schizophrenia, memory and other cognitive abilities are strongly associated with functional outcome. It has been postulated that antipsychotic medication can impair long-term potentiation and cognition by altering dopaminergic transmission. In order to assess the effects of the D2 antagonism of antipsychotics on LTP, we performed a literature review. The results are summarized below and in Table 1.

1. Long-Term Potentiation

1.1 Mechanism

Long-term potentiation refers to the enhancement of signal transmission at a synapse, resulting from the coordinated activity of two or more neurons (Bliss and Lømo 1973; Malenka and Bear 2004). The most common form of LTP is dependent on the N-methyl-D-aspartate (NMDA) receptor (Collingridge and Bliss 1995; Morris 1989). In NMDA receptor-dependent LTP, the timing of glutamate release from the presynaptic terminal in relation to post-synaptic depolarization is essential for inducing potentiation. At resting membrane potential, magnesium ions block the pore of the NMDA receptor so that calcium ions cannot pass through, regardless of glutamate binding. When the post-synaptic neuron is depolarized, magnesium ions are forced out of the receptors. The contemporaneous binding of glutamate along with magnesium ion expulsion from NMDA receptors allows calcium ions to enter the post-synaptic terminal. In this way, the NMDA receptor acts as a coincidence detector for pre- and post- synaptic depolarization (Ascher and Nowak 1988; Collingridge and Bliss 1995). The resulting increase in intracellular calcium concentration activates calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC), triggering a signalling cascade that results in strengthening of the synapse (Ling et al. 2002; Malinow et al. 1989). Calcium dependent adenylyl cyclase activation, which results in the formation of cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A (PKA) and transcription factors, has also been shown to be necessary for LTP induction (Wong et al. 1999; Wu et al. 1995). Signalling through these molecules leads to protein kinase activation and phosphorylation of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which enhances membrane conductance at the synapse (Barria et al. 1997; Soderling and Derkach 2000). Additionally, more AMPA receptors are inserted into the membrane, further increasing conductance (Bliss and Collingridge 1993; Lu et al. 2001; Malenka and Nicoll 1999).

1.2 LTP Induction

Under experimental conditions, LTP is induced by delivering a tetanus to a population of presynaptic neurons using a stimulating electrode. Following tetanization, voltage changes in post-synaptic neurons in response to single-pulses of electrical stimulation are measured using a recording electrode. LTP is quantified by comparing the excitatory post-synaptic

potential (EPSP) slope and the post-synaptic neuron population spike amplitudes in response to single pulses before and after stimulation (Bliss and Lømo 1973).

The induction of LTP can be facilitated by performing experiments in a magnesium-free solution, which removes magnesium ions from NMDA receptors so that calcium ions can enter the postsynaptic terminal unimpeded (Coan and Collingridge 1985).

1.3 Dopamine Modulates LTP

The neurotransmitter dopamine is one of the many modulators of LTP and synaptic function. It is largely found in the nigrostriatal, tuberinfundibular, mesolimbic and mesocortical pathways and exerts its effects by signalling through D1- and D2-like receptor families. D1-like family receptors are coupled to G_s, activate adenylyl cyclase and include the D1 and D5 receptors, whereas D2-like family receptors are coupled to G_i and G_o proteins, which inhibit adenylyl cyclase and include the D2, D3 and D4 receptors (Iversen 1975; Kebabian and Calne 1979). D2-like receptors can enhance excitatory activity by inhibiting the release of the inhibitory neurotransmitter GABA and increasing glutamatergic transmission (Cooper and Stanford 2001; Hu and White 1997; Seamans et al. 2001; Smiałowski and Bijak 1987). Therefore the antagonism of D2 receptors is expected to result in suppression of LTP.

2. Antipsychotics and LTP

2.1 Antipsychotic Mechanism of Action

A common mechanism through which antipsychotic medications alleviate psychotic symptoms is the antagonisms of the D2 receptors (Kapur and Mamo 2003; Seeman et al. 1976). In contrast, antipsychotics have been found to negatively impact cognition (Beuzen et al. 1999; Uchida et al. 2009). Some of the cognitive deficits associated with antipsychotics have been attributed to the D2 antagonism. In particular, a positron emission tomography (PET) cross-sectional study in patients with schizophrenia chronically treated with the antipsychotic risperidone suggested that D2 occupancy higher than 75% is correlated with attention deficits (Uchida et al. 2009). The cognitive deficits observed in medicated persons with schizophrenia are suspected to be due at least in part to abnormal plasticity (Daskalakis et al. 2008; DeLisi 1997). Thus an understanding of the interaction between antipsychotics and LTP could help to explain the basis of some of the cognitive deficits associated with antipsychotic treatment.

2.2 Effect of Typical Antipsychotics on LTP

Twelve studies (Abe et al. 2009a, 2009b; Centonze et al. 2004; Dunwiddie et al. 1982; Finn et al. 1980; Frey et al. 1990; Gemperle et al. 2003; Itsuki Jibiki et al. 1993; Matsumoto et al. 2008; Mody et al. 1984; Xu and Yao 2010; Xu et al. 2009) have investigated the effects of typical antipsychotics on LTP. Eleven of these studies were performed in wild type animals and under physiologic conditions, and one in slices from the brain of mutant mice lacking the dopamine transporter protein.

Among those studies performed in healthy wild-type animals, eight studies found that antipsychotics impair LTP (Abe et al. 2009a, 2009b; Dunwiddie et al. 1982; Finn et al. 1980; Frey et al. 1990; Itsuki Jibiki et al. 1993; Mody et al. 1984; Xu and Yao 2010). In one of these, impairment was reversed when GABAergic neurotransmission was abolished during application of the antipsychotic (Abe et al. 2009b). Two of these studies assessed the effect of antipsychotics on LTP maintenance separately from LTP induction. Both studies found that LTP induction but not maintenance was impaired by antipsychotics (Itsuki Jibiki et al. 1993; Mody et al. 1984), suggesting that only LTP induction can be modulated by D2 antagonists.

In contrast to the eight studies reported above, two found no effect of the typical antipsychotic haloperidol on LTP (Gemperle et al. 2003; Matsumoto et al. 2008) and one found that chronic haloperidol enhanced LTP in the absence of magnesium (Centonze et al. 2004). In the first of these, rat prelimbic cortex slices were bathed in 0.2 μM haloperidol, causing a reduction in EPSP slope prior to tetanization but no impairment in LTP (Gemperle et al. 2003). The concentration of haloperidol used in this study is one to two orders of magnitude lower than brain tissue concentrations of haloperidol - as estimated using radioreceptor assay - achieved in other experiments which demonstrated LTP impairment (Campbell et al. 1980). The low drug concentration is likely responsible for the lack of observed effect. The importance of drug concentration is highlighted in another study using haloperidol, which found that an injection of 1.3 nmol to the basolateral amygdala had no effect on LTP while an injection of 4.4 nmol impaired LTP (Abe et al. 2009a).

In the second study, the intraperitonneal injections of 1 mg/kg haloperidol did not impair LTP in the hippocampus of rabbits (Matsumoto et al. 2008). Another research group performing a similar experiment showed a different effect, reporting impaired LTP (Itsuki Jibiki et al. 1993). Jibiki et al. (1993) administered 0.8 mg/kg or 1.6mg/kg of haloperidol to rabbits and stimulated the hippocampus. While these two studies are similar in many respects, one important difference is the time between haloperidol injection and tetanic stimulation. Matsumoto et al. (2008) allowed 20 min between injection and tetanization, whereas Jibiki et al. (1993) allowed 1 h. Radioreceptor assay experiments have shown that haloperidol level in rat brain tissue rises steeply during the first 30 min after intraperitonneal injection of 1 mg/kg, peaking 1 h post-injection(Campbell et al. 1980; Cohen et al. 1980). Given that haloperidol concentration in the brain is significantly higher after 1 hour than 20 min, this could account for the different results observed by Matsumoto et al.(2008) and Jibiki et al.(1993).

A third study assessed the effects of haloperidol in a magnesium-free solution which is meant to promote LTP (Centonze et al. 2004). In this study, a single intraperitonneal dose of haloperidol had no effect on LTP in a magnesium-free solution, but when administered chronically enhanced it. Given that this study was performed in the absence of magnesium, it is difficult to compare these results to those of experiments performed under physiologic concentrations of magnesium.

Finally, one experiment was performed in a mutant mouse. The study examined the effects of typical antipsychotics in dopamine transporter knock-out mice in order to observe the

actions of haloperidol under hyperdopaminergic conditions. Impaired LTP was seen in the anterior cingulate cortex and prelimbic cortex prior to the administration of haloperidol. Acute haloperidol partially restored LTP and chronic haloperidol restored it fully (Xu et al. 2009). This might be explained by the relationship between dopamine concentration and plasticity. The ideal D2 receptor occupancy has been found to be between 65–80%, with higher or lower occupancy being associated with impaired cognitive function and neuroplasticity (Kapur et al. 1999; Monte-Silva et al. 2009). This inverted-U shaped relationship could explain the LTP impairments seen in hyperdopaminergic conditions.

2.3 Effect of Atypical Antipsychotics on LTP

Sixteen studies have investigated the effects of atypical antipsychotics (Calabresi et al. 1997; Delotterie et al. 2010; Dunwiddie et al. 1982; Frey et al. 1990; Gemperle and Olpe 2004; Gemperle et al. 2003; Kubota et al. 2000, 1996b, 2001, 2002, 2008; Matsumoto et al. 2008; Mody et al. 1984; Molina-Luna et al. 2009; Shim et al. 2012; Xu et al. 2009). Aside from clozapine, these medications were largely found to impair LTP. Six of these were performed in wild-type animals and physiologic ion concentrations using atypical antipsychotics other than clozapine (iloperidone, olanzapine, risperidone, sulpiride and zotepine) (Dunwiddie et al. 1982; Frey et al. 1990; Gemperle et al. 2003; Kubota et al. 2001, 2002; Shim et al. 2012). Four of these reported that atypical antipsychotics impaired LTP (Frey et al. 1990; Gemperle et al. 2003; Kubota et al. 2001, 2002).

One experiment did not find any effect of sulpiride on LTP (Dunwiddie et al. 1982). In contrast, a similar study that used sulpiride found LTP impairment even though the drug concentration was lower by 100-fold (Frey et al. 1990). Both experiments were performed in slices from rat hippocampus. Aside from drug concentration, one difference between these two studies was the time for which responses to single pulses were recorded after tetanic stimulation. Frey et al.'s (1990) observations lasted up to 8 hours, and they noted that sulpiride only inhibited the late phase of LTP, occurring 3 to 4 hours after tetanus. Experiments performed by Dunwiddie et al. (Dunwiddie et al. 1982) only tested for 10 min after tetanus, and so could not have observed impairments in late-LTP.

One study performed in rabbits which were administered 1–2 mg/100 g of olanzapine daily for four weeks found that the drug enhanced LTP for 10 min after administration (Shim et al. 2012). No other studies examined the effects of olanzapine on LTP and the cause of this unexpected result is still elusive. One potential explanation is the antagonisms of olanzapine at the serotoninergic receptors. Serotonin has been found to impair LTP (Corradetti et al. 1992; Kim et al. 2006; Villani and Johnston 1993), and thus by blocking transmission through the serotonin receptor might facilitate potentiation.

Two studies were performed in mutant animals. The first used mice lacking the gene for stable tubule-only polypeptide (STOP), which results in a phenotype with impaired LTP and behaviors that are thought to model symptoms of schizophrenia (Andrieux et al. 2002; Bégou et al. 2008; Fradley et al. 2005; Powell et al. 2007). This study reported that chronic treatment with risperidone did not prevent LTP impairments in these animals whereas chronic clozapine did (Delotterie et al. 2010). In contrast, chronic treatment with both

risperidone and clozapine alleviated deficits in social behaviour and motivation tasks (Delotterie et al. 2010).

The second study used D2-knockout mice and tested them in the presence of Mg (physiologic condition) and in its absence in order to examine the role that D2 receptors play in regulating LTP in the corticostriatal pathway (Calabresi et al. 1997). Whereas high-frequency stimulation in the hippocampus causes LTP, in the corticostriatal pathway it causes LTD by signalling through nitric oxide-producing interneurons. In the absence of magnesium such stimulation results in LTP in the corticostriatal pathway (Centonze et al. 1999). Consistent with these findings, this second study found LTD when stimulating slices from wild-type mice in the presence of Mg, and LTP when stimulating in an Mg-free solution. Conversely, stimulating slices from animals lacking the D2 receptor in the presence of Mg stimulation resulted in LTP. When sulpiride was administered to the wild-type slices bathed in Mg-free solution it significantly increased LTP. Thus, dopaminergic transmission was found to be important in determining whether stimulation to the corticostriatal pathway had excitatory or inhibitory effects on plasticity.

2.3.1 Clozapine—The atypical antipsychotic clozapine had unique and varied effects on potentiation. Of eight studies using clozapine, six were performed in wild-type animals and two in animal models of schizophrenia. Of these six, two found that acute clozapine facilitated LTP (Gemperle et al. 2003; Matsumoto et al. 2008). Three found that clozapine increased EPSP slope and spike amplitude but did not affect the magnitude of potentiation caused by tetanization (Kubota et al. 1996a, 2008, 2000), and one found that chronic but not acute clozapine impaired LTP, though this effect was only significant from 50 to 60 min after tetanization (Gemperle and Olpe 2004). Both studies performed in mutant animals with impaired LTP found that clozapine reversed these deficits (Delotterie et al. 2010; Xu et al. 2009).

One research group performed a series of experiments to examine clozapine-induced potentiation (Kubota et al. 1996a, 2008, 2000). Unlike other antipsychotics, the drug was shown to cause potentiation in the absence of tetanization (Kubota et al. 1996a). While potentiation induced by both clozapine and tetanization were abolished by the NMDA antagonist MK-801, microdialysis experiments showed that clozapine but not tetanization increased extracellular dopamine (Kubota et al. 2008, 2000). Given that clozapine causes dopamine release and that it has a low affinity for D2 receptors compared to other antipsychotics, it is possible that the drug may potentiate EPSP slope and spike amplitude by increasing signalling through agonism at the dopamine receptors(Kubota et al. 2008; Rollema et al. 1997).

2.4 Effects of Other D2 Antagonists on LTP

Three studies investigated effects of D2 antagonists that are not used as antipsychotics. Both domperidone and raclopride were found to impair LTP (Frey et al. 1988, 1990; Molina-Luna et al. 2009). In one of these studies (Molina-Luna et al. 2009), rats were trained to reach through a small window and grasp a food pellet held on a pedestal. Raclopride, sulpiride, or the D1 antagonist SCH23390 injected into the primary motor cortex (area M1) during the

learning phase impaired performance. Sulpiride had no effect when it was administered after the task had been learned (Molina-Luna et al. 2009).

2.5 Chronic Antipsychotic Treatment

Five publications described the effects of chronic antipsychotic treatment, with three of these comparing chronic and acute treatments. One of the three showed that chronic but not acute clozapine impaired LTP in the prefrontal cortex (Gemperle and Olpe 2004). The same group previously found that a higher, acute dose of clozapine enhanced LTP, highlighting the importance of treatment duration on drug effects (Gemperle et al. 2003). The second study found a difference between chronic and acute treatment in the dopamine transporter knockout mouse, which displays impaired LTP. Acute treatment with clozapine or haloperidol partially rescued LTP, while chronic treatment fully rescued it (Xu et al. 2009). In the third study, chronic but not acute treatment with haloperidol facilitated LTP in corticostriatal slices in a magnesium-free solution (Centonze et al. 2004).

One of the two studies that investigated chronic treatment only found that chronic administration of clozapine, but not risperidone, reversed the LTP impairment seen in STOP null mice (Delotterie et al. 2010). The other study found that chronic administration of olanzapine facilitated LTP for 10 min after tetanization in rat hippocampal slices (Shim et al. 2012).

When evaluating the clinical significance of these findings, it is important to note that the half-life of antipsychotics in animals is 2–4 hours, compared to 12–24 hours in humans (Kapur and Mamo 2003). When drugs are administered once or twice per day, as was the protocol for all but two of the long-term studies, the result is that the drug concentrations in the brains of animals drop significantly lower than those in humans during trough periods. As a result, the dosing strategies employed in chronic animal studies are not necessarily an accurate model of long-term use in humans.

3. Implications and Future Work

The vast majority of human and animal studies found that antipsychotics are associated with LTP impairment. Conversely, few found no effect or improvement. Typical and atypical antipsychotics behaved similarly, with the exception of clozapine which caused potentiation independent of tetanization and olanzapine which was found to facilitate tetanus-induced potentiation. The aberrant findings of enhancement or no effect of antipsychotics on LTP can largely be explained by differences in drug concentration in brain tissue, by the physiology of the animals (i.e. mutant vs. wild) in which they were performed or by the receptor binding profile (in particular clozapine vs. others) of the drug.

3.1 Cognitive Effects

The results of these electrophysiology studies are of interest when considering the effects of antipsychotics on cognition. These drugs have been shown to negatively affect attention, memory, and motor control, with attention deficits being correlated with antipsychotic D2 occupancy (Beuzen et al. 1999; Uchida et al. 2009). LTP impairments may be the mechanism through which they exert this effect.

Cognitive ability in people with schizophrenia has repeatedly been shown to be a good predictor of long-term functional outcome (Bowie et al. 2010; Green and King 1996; Green et al. 2004, 2000). Specifically, attention, executive function, and verbal and working memory are strongly correlated with community involvement, social problem solving and skill acquisition. Furthermore, longitudinal studies suggest that cognitive ability can predict functional outcome for periods lasting over 6 months (Green et al. 2000). Minimizing the impairments to cognition due to both the disease and to antipsychotics is an important consideration in treating patients with schizophrenia.

3.2 Implications for Antipsychotic Dosing

Given the deleterious effects of antipsychotics on cognition and in turn on functional outcome, it may be beneficial to reduce as much as clinically possible the patient's dose of these medications. Dose reduction has been found to be beneficial in improving cognitive and negative symptoms. Dose reduction of conventional antipsychotics has been associated with improvements in executive function as measured by performance on the Wisconsin Card Sorting Test as well as in negative symptoms (Kawai et al. 2006). More recently, 31 patients treated with risperidone or olanzapine who underwent a 50% dose reduction showed significant improvements in cognitive function compared to a control group (Takeuchi et al. 2013). Moreover, dose reduction has shown to improve the severity of symptoms as measured by the Clinical Global Impression Schizophrenia and Severity of Illness scales (Suzuki et al. 2003). Our group is currently performing a dose reduction study examining the relationship between D2 receptor occupancy and cognition in older people with schizophrenia [NIH trial 4R01MH084886-04]. While reducing the antipsychotic dose of people with schizophrenia might be a way to mitigate the drugs' harmful effects, it can increase the risk of positive symptom relapse. This is illustrated in one study (Suzuki et al. 2003) where five of 41 participants were unable to tolerate a reduction in their medication dose because they experienced worsening in symptoms.

3.3 Limitations

There are a number of limitations that prevent the studies reviewed here from accurately modelling the effects of antipsychotics in patients with schizophrenia. Drug dosing, duration of drug administration and physiologic changes associated with schizophrenia can alter the observed effect of antipsychotics on LTP. Evidence that dopaminergic transmission (Howes and Kapur 2009) and plasticity (Frantseva et al. 2008; Hasan et al. 2011) are altered in patients with schizophrenia (Delotterie et al. 2010; Xu et al. 2009) suggests that results from wild type animals or healthy humans might not translate to patients with schizophrenia. Only two studies were performed using animal models of schizophrenia. In both cases, LTP was impaired in mutant mice and restored by antipsychotics. These findings raise the question of whether antipsychotics might in fact be beneficial in reversing the LTP impairments present in schizophrenia, while being detrimental to neuroplasticity in healthy animals and humans. Also, the majority of the studies included in our review (20 of the 23) were performed on animals that received acute antipsychotic treatment. Long-term antipsychotic treatment is associated with changes in dopaminergic transmission, which can in turn modify the effect of antipsychotics on LTP. These include changes in D2 receptor affinity, dopamine metabolism and activity of dopaminergic neurons (Bacopoulos et al.

1980; Chiodo and Bunney 1983; Florijn et al. 1997; Silvestri et al. 2000; Stockton and Rasmussen 1996; Tarazi et al. 1997; Wilmot and Szczepanik 1989). Finally, this review focused only on the effects of antipsychotics on dopaminergic transmission, however these medications are also known to affect serotonergic, histaminergic, adrenergic and muscarinic receptors (Richelson and Souder 2000). The effects of antipsychotics on LTP might therefore be a result of their action on other receptors, rather than D2 alone.

In order to best discern the effect that antipsychotic treatment has on plasticity in people with schizophrenia, experimental conditions should approximate the conditions experienced by patients. A review of studies on antipsychotics and LTP shows a dearth of research performed in humans, as only two relevant studies were found (Korchounov and Ziemann 2011; Monte-Silva et al. 2011). These studies used healthy people as participants and found that antipsychotics impaired LTP-like plasticity. Both were performed using transcranial magnetic stimulation (TMS) paradigms; one with paired associative stimulation (PAS) and another with theta-burst stimulation (TBS). In these paradigms, LTP-like plasticity is defined as the potentiation of the motor evoked potential in response to TMS before and after the intervention, i.e. PAS or TBS. In the PAS study, a single dose of haloperidol given to healthy subjects suppressed LTP-like plasticity (Korchounov and Ziemann 2011). In the TBS study, an acute dose of sulpiride given to healthy subjects suppressed the LTP-like effect of intermittent TBS and the long-term depression-like effect of continuous TBS (Monte-Silva et al. 2011).

4. Conclusion

The animal studies reviewed here suggest differences between acute and chronic exposure to antipsychotics. Further experiments performed with human participants would resolve the problem of equivalent dosing in animals and neurophysiologic differences between humans and animals. Thus, longitudinal studies with pre-post design to assess changes in LTP-like activity in response to antipsychotics are needed.

Acknowledgments

We would like to thank the Campbell Family and the Temerty Family for supporting this research at the Centre for Addiction and Mental Health.

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HIGHLIGHTS

- We review the literature on effects of antipsychotics on long-term potentiation
- Most studies showed that acute antipsychotics impair LTP in animals
- In animal models of schizophrenia, LTP was restored by antipsychotics
- Some differences were seen between chronic and acute treatment
- Further chronic studies using patients with schizophrenia are needed

Table 1

Antipsychotics and Long-Term Potentiation in Animals

	Design	Outcome	Conclusions
Finn et al., 1980	- Rat hippocampal slices were perfused with 40 μM trifluoperazine - LTP was induced by delivering a tetanus	- Trifluoperazine inhibited LTP, as measured by percent change of slope of evoked potentials	- Acute administration of trifluoperazine inhibited LTP in hippocampal slices
Dunwiddie et al., 1982	- Rat hippocampal slices were treated with flupentixol (40 μM), sulpiride (100 μM), or trifluoperazine (50 μM or 100 μM) - After tetanus, population spike amplitudes were measured from area CA1	- Trifluoroperazine significantly reduced spike amplitude - Flupentixol also reduced spike amplitude, but to a lesser degree than trifluoperazine - Sulpiride did not cause change in spike amplitude	- Acute administration of trifluoperazine or flupentixol but not sulpiride inhibited LTP in hippocampal slices
Mody et al., 1984	- Rat hippocampal slices were perfused with 10 μM pimozide or 10 μM trifluoperazine during stimulation - LTP was induced by stimulating slices with a tetanus or by exposing slices to a concentrated calcium solution - Population spike amplitudes were measured from area CA1	- Pimozide and trifluoroperazine suppressed potentiation - Pimozide and trifluoroperazine did not affect potentiation when it had been established before perfusion - Similar results were seen when researchers attempted to induce potentiation by increasing calcium concentration in the bathing solution	- Acute administration of pimozide or trifluoperazine inhibited induction but not maintenance of LTP in hippocampal slices
Frey et al., 1988	- Rat hippocampal slices were perfused with the D2 antagonist domperidone (1 μM) - LTP was induced by delivering a tetanus - Domperidone was washed out after the last tetanus - Population spike amplitudes were recorded from area CA1	- Spike amplitude was lower in the domperidone group compared to control starting from the time of the third tetanus (20 min after the first) - Spike amplitude returned to baseline in the domperidone group at 8 h post-tetanus, but was still potentiated in the control group at this time	- Acute administration of domperidone inhibited LTP in hippocampal slices

	Design	Outcome	Conclusions
Frey et al., 1990	- Rat hippocampal slices were bathed with the D1/D2 agonist apomorphine 1 μM), D1/D2 antagonist flupentixol (1 μM), or one of the D2 antagonists domperidone or sulpiride(1 μM for each) - LTP was induced by stimulating slices with a tetanus - Field EPSP and population spike amplitudes were recorded from area CA1	- Domperidone, sulpiride and fluxpenthixol impaired late LTP - Treatment with both domperidone and apomorphine together resulted in normal potentiation	- Acute administration of domperidone, sulpiride or flupentixol impaired late LTP in hippocampal slices
Jibiki et al., 1993	- Rabbits received an injection of haloperidol (0.8 mg/kg or 1.6 mg/kg) 30 min after tetanus or 1 hr before tetanus - LTP was induced by stimulating the perforant path - Field EPSP and spike amplitudes were recorded from the dentate gyrus	- When haloperidol was administered before tetanus, LTP was significantly impaired - Haloperidol administered after the tetanus showed no effect on LTP	- Acute administration of haloperidol impaired induction but not maintenance of LTP in the hippocampus
Kubota et al., 1996	- Rabbits received an injection of either 10 or 20 mg/kg of clozapine 60 min before tetanus - LTP was induced by stimulating the perforant path - Field EPSP and spike amplitudes were recorded from the dentate	- Clozapine had no effect on tetanizationem-induced LTP - In the high-clozapine group, LTP was observed following clozapine administration, before tetanization	- Acute clozapine administration without tetanization caused potentiation in the hippocampus - Tetanization after clozapine administration caused further potentiation. - Clozapine had no effect on tetanus-induced LTP
Calabresi et al., 1997	- Experiments were performed on corticostriatal slices from D2 receptor knockout mice and wild type mice. - Some wild-type slices were perfused with 1μM of L-sulpiride before stimulation. - LTP was induced by stimulating cortical fibers	- Wild type slices in the presence of magnesium showed LTD in response to stimulation, whereas slices from D2R null mice showed LTP.	- Mouse corticostriatal slices lacking D2 receptors showed LTP in response to tetanization, whereas wild-type slices showed LTD.

	Design	Outcome	Conclusions
Kubota et al., 2000	- Rabbits received injections of the NMDA receptor antagonist MK-801 (0.5 mg/kg or 1.0 mg/kg), while 5 control animals received injections of vehicle only - 30 min later, both groups were given clozapine (20 mg/kg) - 60 min after clozapine injections, LTP was induced by stimulating the perforant path	- In the control condition, clozapine caused potentiation. Tetanization caused further potentiation - 0.5 mg/kg of MK-801 had no effect on clozapine- and tetanus-induced potentiation - 1.0 mg/kg of MK-801 blocked clozapine-induced and tetanus-induced potentiation	- A high concentration of NMDA antagonist impaired clozapine-and tetanization-induced LTP in rabbit hippocampus
Kubota et al., 2001	- Rabbits received an injection of risperidone (0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg), or saline 60 min before tetanus - LTP was induced by stimulating the perforant path - Field EPSP and spike amplitudes were recorded from the dentate gyrus	- There was apparent dose-dependent suppression of LTP as indexed by spike amplitudes and EPSP slopes	- Acute administration of risperidone inhibited LTP in rabbit hippocampus
Kubota et al., 2002	- Rabbits received an injection of zotepine (1.0 mg/kg, 2.0 mg/kg, 5.0 mg/kg), or saline (5 in each group) 60 min before tetanus - LTP was induced by stimulating the perforant path - Field EPSP and spike amplitudes were recorded from the dentate	- There was apparent dose-dependent suppression of LTP as indexed by spike amplitudes and EPSP slopes	- Acute administration of zotepine inhibited LTP in rabbit hippocampus
Gemperle et al. 2003	- Rat prelimbic cortex slices were perfused with clozapine (10 μM), haloperidol (0.2 μM), or iloperidone (2.5 μM) - LTP was induced by stimulating slices in layer II - Field EPSP and spike amplitudes were recorded from layer V of the prelimbic cortex	- Clozapine facilitated synaptic potentiation, increasing the duration of potentiation - Haloperidol had no effect on LTP, while iloperidone impaired it	- Acute administration of clozapine facilitated, iloperidone impaired and haloperidol had no effect on LTP in rat prelimbic cortex slices
Centonze et al., 2004	- Rats received either acute (1 injection) or chronic (20 injections) haloperidol (1 mg/kg). Slices were tested in a solution of 1.2 mMol Mg to induce LTD or an Mg-free solution to induce LTP. - Wild-type mice and mice lacking the long and short isoforms, or only the long isoform of the D2 receptor were also tested in 1.2 mM or 0 mM of Mg.	- In rats, HFS in the Mg-free solution induced LTP, whereas in 1.2 mM Mg it induced LTD. Acute haloperidol treatment had no effect,whereas chronic haloperidol treatment prior to stimulation resulted in LTP in both the 1.2 mMol Mg and the Mg-free solutions. - Wild-type and all mutant mice displayed LTP when stimulated in the absence	- Chronic but not acute administration of haloperidol enhanced LTP in corticostriatal slices in a magnesium-free solution by signaling through long isoform D2 receptors

	Design	Outcome	Conclusions
	- LTP was induced with high-frequency stimulation delivered to the excitatory terminals in corticostriatal slices - Motor coordination and behavior were assessed.	of Mg. Chronic haloperidol treatment enhanced LTP amplitude in wild-type but not mutant mice. - Stimulation in the presence of Mg resulted in LTD in wild-type mice but LTP in mutants. There were no significant motor or behavioral effects	
Gemperle and Olpe, 2004	- Rats were administered either acute (1 dose) or chronic (21 doses) of clozapine through drinking water, with the target dose being 30 mg/kg per day - LTP was induced by stimulating layer II of rat prelimbic cortex slices - Field potentials and spike amplitudes were recorded from layer V of the prelimbic cortex	- LTP was impaired, though still present, in the chronic clozapine condition. The difference was only significant in the 50–60 minute post-tetanus period - No difference was observed between control and acute groups	- Chronic administration of clozapine mildly impaired LTP in rat prelimbic cortex - Acute clozapine had no effect
Matsumoto et al., 2008	- Rats were administered 20 mg/kg clozapine or 1 mg/kg haloperidol, as well as 10 μg of either D1 agonist SKF-38393, D1 antagonist SCH23390 or D2 antagonist remoxipride 20 min before tetanization - LTP was induced by two series of HFS of hippocampal area CA1, in-vivo - Population spike amplitude were recorded from medial PFC	- Haloperidol did not affect LTP while clozapine facilitated it. Clozapine-induced potentiation was not observed - The potentiating effect of clozapine was blocked by the D1 receptor antagonist but not by the D2 receptor antagonist - The effect of the D1 agonist on LTP was similar to that of clozapine - Clozapine caused a sustained increase in dopamine level, while tetanization caused a transient increase	- Acute administration of clozapine facilitated LTP through D1 receptor signaling in rat hippocampus. - Haloperidol had no effect on LTP.
Kubota et al., 2008	- One group of rabbits received an injection of clozapine (20 mg/kg) and tetanic stimulation 60 min later, another received clozapine but no tetanic stimulation and a third received tetanic stimulation but no clozapine - LTP was induced by stimulating the perforant path - EPSPs and population spikes were recorded for the duration of the experiment - Extracellular dopamine and 5-HT were measured every 5 min with microdialysis	- In the control, there was no change in extracellular dopamine or 5-HT after tentanization - There was an increase in extracellular dopamine for 60 min following clozapine injection - Tetanization did not significantly affect dopamine level - Neither clozapine injection nor tetanic stimulation affected extracellular 5-HT	- Acute administration of clozapine increased extracellular dopamine but not 5-HT. - Tetanization had no effect on dopamine or 5-HT.

	Design	Outcome	Conclusions
Abe et al., 2009a	- Rats received injections of saline, chlorpromazine (10, 30 or 100 nmol), or haloperidol (4.4 nmol or 13.3 nmol) - Another group of rats underwent either sham surgery or basolateral amygdala lesion and received chlorpromazine (100 nmol) or saline. - A third group of rats underwent either sham surgery or ventral tegmental lesion, and received injections of a D1 agonist or D2 agonist to the basolateral amygdala. - In all experiments, after the intervention, LTP was induced with high frequency stimulation of perforant path - Population spike amplitude was measured from the granule cell layer of the basal ganglia	- Injection of chlorpromazine and haloperidol suppressed LTP in dose-dependent manner - The inhibitory effect of 4.4 nmol of haloperidol was not seen when animals were injected with 3 nmol of D2 agonist quinpirole - Basolateral amygdala lesioned group had impaired LTP. There was no additional impairment due to chlorpromazine. - Haloperidol suppressed LTP in the sham group at 4.4 nmol and 13.3 nmol - Ventral tegmental lesion suppressed LTP, and the injection of aD1 or D2 agonist rescued LTP	- Acute administration of haloperidol suppressed LTP in the basal ganglia by antagonizing D2 receptors. - Dopaminergic transmission from basolateral amygdala enables LTP in the basal ganglia. - Dopaminergic transmission from ventral tegmentum through both D1 and D2 receptors inputs enables LTP in the basal ganglia.
Abe et al, 2009b	- Rats received introcerebral ventricular administration of saline, chlorpromazine (15 nmol), $GABA_A$ antagonist picrotoxin (1mg/kg) or D2 agonist quinpirole (80 nmol) - LTP was induced with either a strong tetanus of 100 pulses at 100 Hz delivered twice 30 s apart or a weak tetanus of 100 pulses at 100 Hz, once - Experimenters stimulated the basolateral amygdala and recorded from the dentate gyrus	- The strong tetanus, but not the weak, induced LTP - Chlorpromazine suppressed LTP after strong tetanic stimulation - When picrotoxin was injected with chlorpromazine no suppression was seen - The injection of either quinpirole or picrotoxin allowed weak stimulation to induce LTP - There was no additive effect when quinpirole and picrotoxin were administered together	- Impairment of hippocampal LTP by chlorpromazine was prevented when GABAergic inhibition was blocked

	Design	Outcome	Conclusions
Molina-Luna et al., 2009	- Experiments were performed on rat cortical slices from area M1 - Slices were bathed with D2 antagonist raclopride or D1 antagonist SCH23390 - LTP was induced with theta burst stimulation - For behavioural experiments, rats performed a motor learning task involving reaching with forlimbs after receiving an injection of raclopride, sulpiride, D1 antagonist SCH23390 or vehicle. Some animals received sulpiride only after task acquisition.	- LTP was significantly impaired by raclopride and SCH23390 - In slices bathed in either antagonist, LTP was still present, although weaker in amplitude - Raclopride, sulpiride and SCH23390 injected in M1 forelimb area during the learning phase of the reaching task lowered success rate - Sulpiride injected after the reaching task had been learned did not affect success rate	- Acute administration of a D2 or D1 antagonist impaired LTP in cortical slices from area M1. - D1 and D2 antagonists impaired skill acquisition of a motor learning task. - After the task had been learned, a D2 antagonist had no effect on performance.
Xu et al., 2009	- Cortical slices from anterior cingulate cortex and/or prelimbic cortex from wild type and dopamine transporter knock-out mice were treated with bath application of haloperidol (10 μM) - LTP was induced with either theta-burst stimulation, tetanic stimulation or paired stimulation - Stimuli were applied to layer II/III of the anterior cingulate or prelimbic cortices and recordings were taken from layer V - In-vivo experiments were performed with wild-type and dopamine transporter knock-out mice that received IP injections of haloperidol (acute dose 1 mg/kg or chronic 0.5mg/kg/day for 14 days), raclopride (3 mg/kg), clozapine (acute dose 6 mg/kg or chronic 4mg/kg/day for 14 days) - In-vivo, LTP was induced using theta burst stimulation with recording electrodes implanted in the right PFC	- For all three induction protocols, LTP was impaired in the knock-out mice compared to controls - Bathing dopamine transporter knockout slices in haloperidol restored LTP - In in-vivo experiments a single haloperidol injection increased potentiation in mutants, however it was not restored to the level of wild type animals. Acute haloperidol had no effect on prefrontal LTP in wild type mice. - Similar effects were seen with acute raclopride and clozapine - Chronic exposure to haloperidol or clozapine fully restored LTP in knock-out mice.	- LTP is impaired in hyperdomapinergic conditions. This impairment is partially reversed by acute haloperidol, raclopride or clozapine but not by D1 blockade. - Chronic treatment with clozapine or haloperidol fully restored LTP in hyperdopaminergic conditions.
Delotterie et al., 2010	- STOP null mice received risperidone in drinking water (0.1 or 0.3 mg/kg/day) or clozapine (1 or 3 mg/kg/day) injected intraperitoneally for four weeks - Four behavioural tests were performed: Y maze test, social investigation test, marble burying test, forced swim test - LTP was investigated in hippocampusof knockout or	- STOP null mice were impaired on all behavioral tests. Deficits on the social investigation test as well as some cognitive deficits were alleviated by chronic risperidone or clozapine. - STOP null mice showed impairments in LTP compared to wild type - High clozapine dose significantly improved	- Chronic administration of clozapine, but not risperidone, reversed the LTP impairment seen in STOP null mice

	Design	Outcome	Conclusions
	control animals who had been administered either clozapine (IP injection of either 3 or 10 mg/kg/day) or risperidone - LTP was induced by theta burst stimulation	LTP in knockout mice, but low dose did not - Risperidone did not improve LTP	
Xu and Yao, 2010	- Mouse PFC slices were bathed in dopamine (100 μM) and/or haloperidol (2 μM), D2 agonist quinpirole (10 μM) - LTP was induced by paired stimulation - Prefrontal corex slices were stimulated in layer II/III and EPSPs were recorded from layer V pyramidal neurons	- Paired stimulation did not induce LTP in controls but did induce LTP in slices bathed in dopamine - Administering haloperidol with dopamine abolished LTP - Quinpirole had a similar effect to dopamine on LTP induction	- Dopaminergic transmission through D2 receptors enables LTP induction in mouse PFC slices. - Acute administration of haloperidol impaired LTP
Shim et al., 2012	- Rats were administered olanzapine (1–2 mg/100 g body weight daily for 4 weeks) in water or lithium in rat chow - LTP was induced by tetanic stimulation to slices from area CA1 of rats	- Lithium facilitated LTP for over 60 min - Olanzapine facilitated LTP for first 10 min following tetanization. The effect diminished over time until there was no difference from control after 50 min	- Chronic administration of olanzapine facilitated LTP for 10 min after tetanization in rat hippocampal slices

Abbreviations: EPSP – excitatory post-synaptic potential, GABA – gamma-Aminobutyric acid, LTD – long-term depression, LTP – long term potentiation, NMDA – N-methyl-D-aspartate, PFC – prefrontal cortex, STOP - Stable tubule-only polypeptide