Eur Neuropsychopharmacol. Author manuscript; available in PMC 2013 August 20.

Published in final edited form as:
Eur Neuropsychopharmacol. 2013 August ; 23(8): 799–813. doi:10.1016/j.euroneuro.2013.05.006.

The potential role of dopamine D_3 receptor neurotransmission in cognition

Shinichiro Nakajima[a,b,c,d], **Philip Gerretsen**[a,b,c,e], **Hiroyoshi Takeuchi**[c,d,f], **Fernando Caravaggio**[a,e], **Tiffany Chow**[b,c,g,h,i], **Bernard Le Foll**[c,i,j,k,l], **Benoit Mulsant**[b,c,i], **Bruce Pollock**[b,c,i], and **Ariel Graff-Guerrero**[a,b,c,i,*]

[a]Multimodal Imaging Group—Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, Canada M5T 1R8

[b]Geriatric Mental Health Program, Centre for Addiction and Mental Health, Toronto, Canada

[c]Department of Psychiatry, University of Toronto, Toronto, Canada

[d]Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan

[e]Institute of Medical Science, University of Toronto, Toronto, Canada

[f]Schizophrenia Division/Complex Mental Illness Program, Centre for Addiction and Mental Health, Toronto, Canada

[g]Rotman Research Institute, Baycrest, Toronto, Canada

[h]Department of Medicine, Division of Neurology, University of Toronto, Toronto, Canada

[i]Campbell Research Institute, Centre for Addiction and Mental Health, Toronto, Canada

[j]Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, Toronto, Canada

[k]Department of Family and Community Medicine, Pharmacology and Toxicology, University of Toronto, Toronto, Canada

[l]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada

Abstract

Currently available treatments have limited pro-cognitive effects for neuropsychiatric disorders, such as schizophrenia, Parkinson's disease and Alzheimer's disease. The primary objective of this work is to review the literature on the role of dopamine D_3 receptors in cognition, and propose dopamine D_3 receptor antagonists as possible cognitive enhancers for neuropsychiatric disorders. A literature search was performed to identify animal and human studies on D_3 receptors and

*Corresponding author. Tel.: +1 416 535 8501x4834; fax: +1 416 583 1284.

Contributors

S. Nakajima and A. Graff-Guerrero lead study design, literature review and interpretation and manuscript preparation. P. Gerretsen, H. Takeuchi, F. Caravaggio, T. Chow, B. Le Foll, B. Mulsant and B. Pollock contributed to the interpretation of the results. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

cognition using PubMed, MEDLINE and EMBASE. The search terms included “dopamine D_3 receptor” and “cognition”. The literature search identified 164 articles. The results revealed: (1) D_3 receptors are associated with cognitive functioning in both healthy individuals and those with neuropsychiatric disorders; (2) D_3 receptor blockade appears to enhance while D_3 receptor agonism seems to impair cognitive function, including memory, attention, learning, processing speed, social recognition and executive function independent of age; and (3) D_3 receptor antagonists may exert their pro-cognitive effect by enhancing the release of acetylcholine in the prefrontal cortex, disinhibiting the activity of dopamine neurons projecting to the nucleus accumbens or prefrontal cortex, or activating CREB signaling in the hippocampus. These findings suggest that D_3 receptor blockade may enhance cognitive performance in healthy individuals and treat cognitive dysfunction in individuals with a neuropsychiatric disorder. Clinical trials are needed to confirm these effects.

Keywords

Dopamine D3 receptor; Cognition; Dopamine D3 receptor antagonist

1. Introduction

Cognition involves a number of mental processes that include attention, memory, language comprehension and expression, problem solving, and decision making. Cognition is indispensable for understanding information, applying knowledge, and changing preferences. Cognitive dysfunction is common in individuals with neuropsychiatric disorders, such as schizophrenia, mood disorders, Parkinson’s disease (PD), autism and Alzheimer’s disease (AD), even though the characteristic manifestations and pathophysiology of these disorders are different (Millan et al., 2012). Importantly, cognitive dysfunction has a negative impact on social functioning, independent community living, employment and quality of life (QOL) (Demirtas-Tatlidede et al., 2013; Green, 2007; Green et al., 2000, 2004; Millan et al., 2012). As such, the discovery of effective treatments to improve cognition is essential for improving QOL in individuals with neuropsychiatric disorders.

Although pro-cognitive drugs, such as donepezil (a cholinesterase inhibitor) or memantine (a weak N-methyl-D-aspartate receptor antagonist), are clinically available for AD, these agents have only short-term effects on behavioral and cognitive test scores compared with placebo (Kaduszkiewicz et al., 2005; McShane et al., 2006; Saddichha and Pandey, 2008). No disease-modifying effects have been shown in AD and no preventative treatments exist (Ballard et al., 2011). Many candidate pro-cognitive drugs have been investigated in clinical trials for schizophrenia, including AZD3480 (an α4β2 central neuronal nicotinic receptor agonist) (Velligan et al., 2012), dimebon (a serotonin 5HT-6 receptor antagonist) (Morozova et al., 2012), EVP-6124, TC-5619 (α7 nicotinic receptor partial agonists) (Lieberman et al., 2013; Prickaerts et al., 2012; Tregellas et al., 2011), rimonabant (a cannabinoid-1 receptor antagonist) (Boggs et al., 2012), and rosiglitazone (a peroxisome proliferator-activated receptor-γagonist) (Yi et al., 2012). Unfortunately, these drugs lack enough efficacy for

therapeutic utilization. Thus, there is an urgent need to identify new therapeutic strategies for cognitive dysfunction in neuropsychiatric disorders.

The dopaminergic (DAergic) system has been implicated in cognitive function through animal and human research, including studies of molecular genetics and neuroimaging (Backman et al., 2006; Cole et al., 2012). Interestingly, animal and human studies have demonstrated that there is an inverted-U curve between DAergic signaling and cognition, where too little or too much DAergic signaling impairs cognitive performance. Mid-level DAergic signaling appears necessary for optimal cognitive performance (Baunez and Robbins, 1999; Boussaoud and Kermadi, 1997; Cools and D'Esposito, 2012; Glickstein et al., 2005).

The present article reviews the data on dopamine (DA) D_3 receptors as a target for novel pro-cognitive treatments. Initially, the role of the DAergic system in cognition is presented. Then, the D_3 receptor predominant brain regions related to cognitive function are discussed, in particular, the limbic regions that modulate memory, emotions and motivation (Gurevich and Joyce, 1999; Murray et al., 1992, 1994). Next, the characteristics and in vivo quantification of D_3 receptors are described and the relationship between D_3 receptors and cognition from previously reported animal and human studies are reviewed. Finally, D_3 receptor antagonists are proposed as a pro-cognitive therapy for cognitive dysfunction in individuals with neuropsychiatric disorders.

2. Search strategies and selection criteria

PubMed, Medline, EMBASE and references from relevant studies, review articles and books were searched using the terms 'dopamine,' 'D3 receptor' and 'cognition.' Only publications written in English pertaining to the relationship between D_3 receptors and cognition were selected. The search yielded 164 articles, which formed the empirical basis of this review. The last search was conducted on April 14, 2013. Cross-referencing of the identified publications was also performed. The literature search was conducted independently by two of the authors (S.N. and A.G.).

3. Characteristics and in vivo quantification of dopamine D_3 receptors

Dopamine receptors are divided into two subclasses, D_1- and D_2-like receptor families. The D_1-like receptor family contains the D_1 and D_5 receptors, and the D_2-like receptor family contains the D_2, D_3, and D_4 receptors (Ilani et al., 2001; Le Foll et al., 2009). As a member of the D_2-like receptor family, D_3 is a G-protein coupled receptor (GPCR). In the simplest conceptualization, GPCRs work as a switch. When a G-protein is attached to the cellular side of a GPCR, the GPCR exists in high-affinity for its ligand, but when the G-protein detaches from the GPCR, the GPCR has very low affinity for DA. D_3 receptors are unique among the D_2-like receptors, exhibiting sustained high affinity for DA (>20-fold higher than D_2 receptors), suggesting that D_3 receptors in vivo may be occupied by endogenous DA for extended periods of time, leading to high spontaneous activation of D_3 receptors (Richtand et al., 2001; Vanhauwe et al., 2000). Unlike D_2 receptors, D_3 receptors can be stimulated by tonic DA levels in the brain due to their high affinity for DA (Sokoloff et al., 1990), and may

attenuate any effects of DA fluctuation related to phasic DA release. Accordingly, small changes in the number or function of D_3 receptors may lead to dramatic effects on synaptic transmission, suggesting that D_3 receptors could be critical modulators of normal DAergic function, and consequently, cognition (as described below). Other DA receptors such as D_1, D_2, D_4 and D_5 are also involved in cognition. As the focus of this review is D_3 receptors and cognition, please see El-Ghundi et al. (2007), Floresco and Magyar (2006), and Takahashi et al. (2012) for a review on other DA receptors and cognition.

D_3 receptors are expressed both as autoreceptors on DA neurons and as post-synaptic receptors (Diaz et al., 1995, 2000; Levesque et al., 1992). They are present in the ventral striatum (nucleus accumbens (NAc)) and other limbic areas (Bouthenet et al., 1991; Sokoloff et al., 1990). There are low D_3 receptor levels in the dorsal striatum and a variety of cortical regions, including the frontal cortex in humans (Hall et al., 1996; Suzuki et al., 1998) and nonhuman primates (Morissette et al., 1998); whereas the dorsal striatum is almost entirely devoid of D_3 receptor expression in rodents. D_3 receptors are also found in the islands of Calleja and cerebellum (Diaz et al., 2000; Levesque et al., 1992). It is important to note that there are significant inter-species differences in the distribution of D_3 receptors in the central nervous system, which may limit generalization of D_3 receptor-mediated behaviors from one species to another (Levant, 1998).

Some of the brain structures expressing D_3 receptors encompass a proposed feedback loop for modulating attention, memory, emotions, motivation and reward. The output neurons of the NAc have a high density of D_3 receptors and receive DAergic innervation from the ventral tegmental area (VTA). The outputs of the NAc reach the entorhinal and prefrontal cortices (PFC) after relaying in the ventral pallidum and mediodorsal thalamus. In turn, the shell of the NAc receives projections from the cerebral cortex, hippocampus and amygdala and projects to the VTA (Sokoloff et al., 2006). The D_3 receptors in the VTA and substantia nigra may function as autoreceptors and affect DAergic feed-forward loops; potentially influencing theta oscillations that seem essential for coordinating neuronal activity among these loops (Fujisawa and Buzsaki, 2011). These feed-forward loops have a unique configuration, and the preferential distribution of D_3 receptors in the regions that modulate attention, memory and emotions (Gurevich et al., 1997) suggests that D_3 receptors may play a role in regulating cognitive function.

Our group has developed [^{11}C]-(+)-4-propyl-9-hydroxy-naphthoxazine ([^{11}C]-(+)–PHNO) (Wilson et al., 2005), the only available radiotracer for imaging D_3 receptors with a 53-fold D_3/D_2 receptor selectivity in vivo in humans (Gross and Drescher, 2012). [^{11}C]-(+)–PHNO is a $D_{2/3}$ PET agonist with high in vitro affinity for both D_2 and D_3 receptors, but shows preferential in vivo affinity and selectivity for D_3 receptors in D_3-receptor brain regions. PET studies in mice and baboons using [^{11}C]-(+)-PHNO in the presence and absence of a D_3 receptor antagonist, SB-277011, confirm that D_3 receptors are highly expressed and quantifiable in vivo in the ventral pallidum, substantia nigra, thalamus, and habenula; to a lesser extent in the ventral striatum; and negligibly in the dorsal caudate and putamen (Rabiner et al., 2009). The development of [^{11}C]-(+)-PHNO as a D_3 receptor PET ligand provides the possibility of in vivo exploration of the role of D_3 receptors in normal and abnormal cognition. The use of [^{11}C]-(+)-PHNO, however, is limited by its non-selective

binding to both D_3 and D_2 receptors, chiefly because D_2 receptors tend to prevail in brain regions where there is an abundance of D_3 receptors (Gurevich and Joyce, 1999; Suzuki et al., 1998). The binding of the [^{11}C]-(+)-PHNO may also be influenced by endogenous DA levels due to its higher affinity for D_3 receptors, especially in the presence of compounds that block auto-receptors, which enhance endogenous DA release (Gross and Drescher, 2012). Thus, a highly selective D_3 receptor antagonist PET tracer is still needed as [^{11}C]-(+)-PHNO may not be a suitable radiotracer to detect D_3 receptors in areas with low D_3 receptor concentrations or in regions where D_2 receptors prevail over D_3 receptors.

The relationship between cognition and D_3 receptors in healthy individuals is inconsistently reported (Ball et al., 1998; Czermak et al., 2009; Keri et al., 2005; Lane et al., 2008). While the D_3 receptor gene, DRD3, was not associated with enhanced general cognitive ability or reasoning skill (Ball et al., 1998; Gong et al., 2011), the DRD3 Ser/Ser genotype was linked to fewer perseverative errors during the Wisconsin Card Sorting Test (WCST) (Lane et al., 2008). In contrast, elderly individuals carrying the DRD3 Ser/Gly genotype had more benefit from multimodal cognitive training than the carriers of the Ser/Ser genotype (Pieramico et al., 2012). Only one study has directly investigated whether differences in midbrain D_3 receptor availability are associated with functional interactions between large-scale networks and brain regions involved in cognition in healthy individuals (Cole et al., 2012). Combining [^{11}C]-(+)-PHNO PET and resting-state functional magnetic resonance imaging (fMRI), this study of healthy individuals demonstrated that high midbrain D_3 receptor availability is associated with reduced functional connectivity between the orbitofrontal cortex (OFC) and frontopar-ietal networks, which are implicated in executive control and salience processing (Seeley et al., 2007). This result suggests that D_3 receptor availability can modulate the pathway underlying cognitive control in healthy individuals.

4. Potential mechanisms between dopamine D_3 receptors and cognition

The preclinical evidence suggests that D_3 receptors influence cognition by modulating PFC function despite the relatively few D_3 receptors in this region (Loiseau and Millan, 2009; Watson et al., 2012a). PET studies of baboons have shown that D_3 receptor-mediated regional cerebral blood flow responses are restricted to the prefrontal and limbic cortices (Black et al., 2002). Executive function as measured with a PFC-dependent task is enhanced in D_3 receptor knockout (KO) mice and is accompanied by increased c-*fos* expression in the PFC (Glickstein et al., 2005). Bilateral microinjection of D_3 receptor antagonists into the PFC of rats improves social recognition, social discrimination and object recognition, while microinjection into the NAc or striatum has no effect (Loiseau and Millan, 2009; Watson et al., 2012a). Moreover, the blockade of D_3 receptor enhances the release of acetylcholine (ACh) in the PFC of rats (Gobert et al., 1995; Lacroix et al., 2003, 2006; Millan and Brocco, 2008; Millan et al., 1995, 2007), whereas D_3 receptor agonists do not increase ACh levels (Gobert et al., 2003). The mechanism by which D3 antagonism results in elevated cortical ACh levels is unclear. Given a high expression of D_3 receptors in the thalamus and a lack of D3 receptor expression in the PFC, modulation of thalamocortical projections via D3 antagonism may indirectly enhance the release of ACh in the PFC. This, in turn, may facilitate the PFC's top-down control of subcortical brain regions that process cognitive cues

(Loiseau and Millan, 2009; Millan et al., 2007; Perio et al., 1989; Soffie and Bronchart, 1988; Watson et al., 2012a; Winslow and Camacho, 1995).

DAergic system enhancement by D_3 receptor antagonists may contribute to the cognitive control exerted by the frontal cortex through other mechanisms (Sesack and Grace, 2010). D_3 receptor KO mice have extracellular levels of DA in the NAc that are twice as high as those of wild type (WT) mice (Joseph et al., 2002; Koeltzow et al., 1998; Le Foll et al., 2005a). Low, D_3-selective doses of preferential D_3 receptor agonists decrease DA synthesis measured by microdialysis in the mesolimbic area in rats (Pugsley et al., 1995). The antisense mutation of D_3 receptors increases DA turnover in the limbic forebrain and NAc in rats (Nissbrandt et al., 1995). In contrast, selective D_3 receptor antagonists block the inhibitory effect of D_3 receptor agonism on DA release and synthesis in the frontal cortex (Banasikowski et al., 2010; Gobert et al., 1995, 1996; Millan et al., 2008). Lastly, a combined PET-fMRI study showed that high mid-brain D_3 receptor availability was associated with reduced functional connectivity between the OFC and frontoparietal networks implicated in executive control in healthy individuals (Cole et al., 2012). These findings suggest that D_3 receptors can modulate cortical control of cognitive functions via their inhibitory effect on mesocortical DAergic activity (Gross and Drescher, 2012). Further work is needed to elucidate the mechanism of the relationship between D_3 receptors, the frontal cortex and cognition, as the PFC has relatively few D_3 receptors. A recent study reported that D_3 receptors may control N-methyl-D-aspartate (NMDA) receptor signaling by acting on pyramidal cells either directly at post-synaptic levels in the NAc or indirectly at presynaptic levels in the PFC. The D_3 receptor selective antagonist, F17141, reversed hyperactivity and social interaction deficits induced by NMDA receptor blockade by MK-801 in mice (Sokoloff et al., 2013). Thus, glutamatergic–D_3 receptor interactions may shed light on these relationships.

Another potential mechanism by which D_3 receptor antagonists may improve cognition is cAMP/PKA/CREB signaling in the hippocampus, which has a modest density of D_3 receptors (Basile et al., 2006; Bouthenet et al., 1991; Khan et al., 1998; Richtand et al., 1995; Stanwood et al., 2000). D_3 receptor antagonists do not appear to influence ACh levels in the hippocampus as they do in the PFC (Bouthenet et al., 1991; Joyce, 2001; Joyce and Millan, 2005; Stanwood et al., 2000). Aged D_3 receptor KO mice showed better spatial memory performance than age-matched WT mice along with a higher degree of hippocampal CREB phosphorylation, which may have neuroprotective effects on memory consolidation (Lee et al., 2005). Whereas no difference was found in the level of CREB phosphorylation in the PFC between the aged D_3 receptor KO mice and age-matched WT mice (Swant et al., 2008; Taubenfeld et al., 1999; Walton et al., 1999; Xing et al., 2010b). Thus, the cognitive effects of D_3 receptors may be attributable to the activation of cAMP/PKA/CREB signaling in the hippocampus.

Alternatively, given that D_3 receptor stimulation potentiates D_1 receptor-mediated behavioral effects (Le Foll et al., 2009; Marcellino et al., 2008), the interaction between D_3 and co-expressed D_1 receptors may cause dysregulation of CREB signaling in the aged hippocampus (Xing et al., 2010b). In support of this, D_1 receptor KO mice do not acquire spatial memory or show activation of the underlying CREB signaling pathways compared to

the WT mice; however, D_3 receptor KO mice exhibited normal learning abilities and normal activation of these signaling pathways. The results suggest that D_1 receptors, but not D_3 receptors, may be critical for hippocampus-dependent spatial learning.

In summary, the above findings suggest that D_3 receptors may influence cognition by modulating PFC function (Loiseau and Millan, 2009; Watson et al., 2012a) and by regulating CREB signaling in the hippocampus (Xing et al., 2010b); however, further research into this relationship is required.

5. Dopamine D_3 receptors and cognition in neuropsychiatric disorders with cognitive dysfunction

Dopamine D_3 receptors are implicated in the pathophysiology of neuropsychiatric disorders that are commonly accompanied by cognitive dysfunction, including schizophrenia (Dubertret et al., 1998; Gross and Drescher, 2012; Keefe and Harvey, 2012), drug addiction (Khaled et al., 2010; Le Foll et al., 2002, 2003, 2005b), PD (Bezard et al., 2003; Boileau et al., 2009), dementia (Sokoloff et al., 2006), mood disorders (Sokoloff et al., 2006), and autism (de Krom et al., 2009), although not consistently (Chiaroni et al., 2000; Cosentino et al., 2009; Heidbreder and Newman, 2010; Kim et al., 2008; Kumar and Patel, 2007; Serretti et al., 2000). However, only a few studies have directly explored the relationship between D_3 receptors and cognition in these conditions.

5.1. Dopamine D_3 receptors in Alzheimer's disease

Dementia is associated with D_3 receptor anomalies. Piggott et al. (1999) demonstrated that D_3 receptor binding is increased in the striatum of AD when compared to healthy controls in a [3H]-7-OH-DPAT autoradiography study of postmortem brains. Preclinical studies have found that the brains of D_3 receptor KO mice have reduced levels of neurofibromin (NF1). The heterozygous loss of NF1 causes neurofibromatosis type I disease and increases amyloid precursor protein (APP) levels, which are involved in the pathogenesis of AD. These findings suggest that a link between NF1, APP and D_3 receptors may contribute to cognitive dysfunction in spatial learning and memory in neurofibromatosis type 1 disease (Castorina et al., 2011; Donarum et al., 2006).

5.2. Dopamine D_3 receptors in schizophrenia

Some genetic and postmortem studies have shown elevated D_3 receptor expression in the central nervous system and blood lymphocytes in individuals with schizophrenia (Gurevich et al., 1997; Ilani et al., 2001). Our group found no difference in D_3 receptor availability as measured with [^{11}C]-(+)-PHNO PET between unmedicated individuals with schizophrenia and healthy controls. The limitations of [^{11}C]-(+)-PHNO are described in the section "Characteristics and in vivo quantification of dopamine D3 receptors" (Graff-Guerrero et al., 2009).

A few studies have explored the relationship between cognitive performance and DRD3 Ser9Gly polymorphisms in individuals with schizophrenia. Szekeres et al. (2004) found that Ser/Ser carriers perform better on the WCST than Gly carriers, which is indicative of better

working memory performance. Keri et al. (2005) found that Gly carriers have more efficient striatal habit learning both in healthy controls and in individuals with schizophrenia. In contrast, Bombin et al. (2008) showed that Ser/Ser carriers perform better on an executive functioning task than Gly/Gly carriers. Conversely, Rybakowski et al. (2005) did not find any association between working memory and the various DRD3 polymorphisms. Given the fact that the Ser allele is associated with a lower affinity for DA than the Gly allele (Jeanneteau et al., 2006; Lundstrom and Turpin, 1996; Lundstrom et al., 1998), these results indicate that the lower DRD3 Ser/Ser affinity for DA and higher DA-mediated response may be associated with better frontal/executive functioning, such as set-shifting.

5.3. Dopamine D_3 receptors in addictions

Dopamine D_3 receptors may play an important role in the pathophysiology of substance use disorders. D_3 receptors are distributed in the mesolimbic DA system where they may mediate the influence of drug-associated cues on drug-seeking behaviors (for reviews, please see Heidbreder (2013); Heidbreder et al. (2005)). A PET study found that methamphetamine polydrug abusers had higher [^{11}C]-(+)-PHNO binding in the D_3 receptor-rich regions, indicating that the D_3 receptor might be upregulated in this population (Boileau et al., 2012).

Few studies have explored the relationship between cognitive function and DRD3 Ser9Gly polymorphisms in individuals with substance use disorders. An association was found between a single nucleotide polymorphism of the DRD3 gene (rs6280TC) and cognitive dysfunction in human immunodeficiency virus (HIV)-positive individuals who were dependent on methamphetamine (Gupta et al., 2011). The study found that DRD3 Gly allele carriers have more cognitive dysfunction than the Ser/Ser carriers in the presence of recent methamphetamine use. Although no association was found between the DRD3 gene and HIV viral load in this study, simian models of the neurological complications of acquired immune deficiency syndrome showed that methamphetamine administration may increase the viral load in the frontal lobe, caudate, and hippocampus (Marcondes et al., 2010). It was proposed that DA enhances replication of the HIV virus in macrophages within the central nervous system. Due to the Gly allele's higher affinity for DA than the Ser allele, the presence of Gly may facilitate increased replication of the virus by methamphetamine, which, in turn, may induce greater cognitive dysfunction. Further research is required to determine the utility of DRD3 genotype as a biological marker in clinical settings.

The relationship between DRD3 and cognition has also been explored in alcohol-dependent subjects. Homozygosity for the DRD3 Ser9Gly polymorphism is significantly increased in alcohol-dependent individuals with low cognitive impulsiveness. Impulsivity secondary to alcohol intoxication may, in part, be related to increased DAergic activity, which was proposed to foster dependence in individuals with low cognitive impulsiveness (Limosin et al., 2005).

In summary, the findings from the few post-mortem, neuroimaging, and genetic studies point to a relationship between D_3 receptors and cognitive dysfunction in individuals with neuropsychiatric disorders.

6. Pharmacological dopamine D_3 receptor intervention and cognition in humans

Few data have been published on the effects of selective DA D_3 receptor antagonists on cognitive dysfunction in humans due to the lack of selective D_3 receptor antagonists available on the market. Although many antipsychotics have high affinity for D_3 as well as D_2 receptors, the high affinity of endogenous DA for D_3 receptors has been postulated to result in only minimal or no D_3 receptor occupancy by antipsychotics in DA rich areas (Graff-Guerrero et al., 2009; Gross and Drescher, 2012; Mizrahi et al., 2011; Schotte et al., 1996). Mugnaini et al. (2013) demonstrated that abstinent smokers took significantly longer to color-name words related to smoking than to color-name neutral control words in the Stroop test (Mugnaini et al., 2013). This attentional bias of the abstinent smokers was partially reversed by a selective D_3 receptor antagonist, GSK598809. ABT-925 is the only selective D_3 receptor antagonist that has survived for testing in a clinical phase II trial in individuals with schizophrenia. Although it did not show significant clinical improvement, positive effects were found in individuals with the G allele of the DRD3 Ser9Gly polymorphism (Bhathena et al., 2011). Further, ABT-925 showed significant effect on executive function and emotion recognition in the same sample (Gross et al., 2013). Most of the evidence is derived from the effects of preferential D_3 receptor-agonists, pramipexole (5- to 7-fold D_3/D_2 and D_4 receptor selectivity) (Brusa et al., 2003; Hubble, 2000; Rektorova et al., 2005; Samuels et al., 2006a, b, 2007) and rotigotine (20-fold D_3/D_2 and 100-fold D_3/D_1 receptor selectivity) (Bunten and Happe, 2006; Sanford and Scott, 2011; Scheller et al., 2009) on cognition in healthy individuals and those with PD or bipolar disorder. Thus far, the cognitive effects of preferential D_3 receptor agonists in humans are mixed (Brusa et al., 2005). Rotigotine, for example, did not significantly influence cognition in individuals with PD (Trenkwalder et al., 2011); while pramipexole improved working memory in individuals with cognitively-impaired PD (Costa et al., 2009) and euthymic bipolar disorder (Burdick et al., 2012). In other studies, pramipexole had deleterious or no effects on working memory in healthy individuals (Ersche et al., 2011; Hamidovic et al., 2008) and impaired reversal learning in individuals with PD (Cools et al., 2006). Moreover, ropinirole (10-fold D_3/D_2 and D_4 receptor selectivity) induced cognitive adverse events less frequently than pramipexole in individuals with early PD (Zagmutt and Tarrants, 2012). These inconsistent findings may derive from the fact that preferential D_3 receptor agonists have other mechanisms, such as 5-HT_{1A} agonism (e.g., rotigotine). Further, preferential D_3 receptor agonists can contribute to excess DAergic activity based on the baseline DAergic activity, which may have negative effects on cognitive function. For example, in individuals with PD there was an inverted U-shaped curve relationship between DAergic signaling and cognition (Svenningsson et al., 2012).

7. Pharmacological dopamine D_3 receptor intervention and cognition in animals

Numerous animal studies have explored the cognitive effects of pharmacological interventions targeting D_3 receptors. Table 1 summarizes the cognitive domains that have been investigated. Interventions have included both D_3 receptor agonists and antagonists

(Gross and Drescher, 2012). Cognitive dysfunction was produced through several distinct perturbations, including the use of drugs such as scopolamine, inter-trial intervals, isolation rearing, and aging. D_3 receptor antagonists either enhanced or had no impact on cognitive performance, including the agents S33084 (Loiseau and Millan, 2009), S33138 (Millan and Brocco, 2008), SB277011 (Loiseau and Millan, 2009), (+)S14297 (Millan et al., 2007), nefadotride (Sigala et al., 1997), RGH-1756 (Laszy et al., 2005), U-99194A (Laszy et al., 2005), and RG-15 (Gyertyan et al., 2008). In contrast, the D_3 receptor agonists impaired cognitive performance in WT mice, including PD128907 (Watson et al., 2012a) and 7-OH-DPAT (Bernaerts and Tirelli, 2003). Moreover, the D_3 receptor antagonist, S33138, reversed age-related cognitive decline in a delayed matching-to-sample task of working memory in old rhesus monkeys, suggesting that D_3 receptor blockade is pro-cognitive independent of age (Millan et al., 2010). The specificity of D_3 receptors for their pro-cognitive effects is supported by the failure of L741,626, a preferential D_2 antagonist, to improve cognition after it was infused in the frontal cortex (Loiseau and Millan, 2009).

D_3 receptors may also participate in the DA-related pro-cognitive effects of angiotensin AT4 receptor agonists through unclear mechanisms (Braszko, 2010). A partial $D_{3/2}$ receptor agonist that preferentially binds to presynaptic receptors abolished the memory-enhancing effects of angiotensin AT4 receptor agonists (Stragier et al., 2007).

In summary, animal studies suggest that D_3 receptor blockade enhances cognitive function, while D_3 receptor activation impairs cognition independent of age, which would justify clinical trials to examine the effect of D_3 receptor antagonists on neuropsychiatric disorders (Laszy et al., 2005).

8. Genetic dopamine D_3 receptor intervention (D_3 receptor knockout) and cognition in animals

The performance of D_3 receptor KO mice on various cognitive tasks, such as the two-choice perceptual discrimination test, SND, the step-through passive-avoidance test, T-maze and the delayed alternation test, were also examined to further characterize the roles of the D_3 receptor (Table 2) (Chourbaji et al., 2008; Glickstein et al., 2002, 2005; Micale et al., 2010; Watson et al., 2012a; Xing et al., 2010b).

D_3 receptor KO mice showed better set-shifting and social discrimination than WT mice (Glickstein et al., 2005; Watson et al., 2012a). While the D_3 receptor antagonist, S33084, improved social discrimination in WT mice, it had no effect on the performance of the D_3 receptor KO mice (Watson et al., 2012a). This suggests that S33084-mediated improvement can be explained by D_3 receptor antagonism, and not by other non-specific effects of S33084. In addition, a stereological assessment of the set-shifting test-induced neuronal expression of c-*fos* in the anterior cingulate and prelimbic/infralimbic cortices revealed higher activation in the D_3 receptor KO mice than in the WT mice (Glickstein et al., 2005). These findings indicate that the increased set-shifting performance in the D_3 receptor KO mice correlates with the magnitude of the activation of the PFC.

Aged D_3 receptor KO mice displayed ameliorated age-related spatial memory dysfunction and smaller decreases in hippocampal CREB activation in comparison with aged WT mice (Xing et al., 2010b). Given that CREB may have neuroprotective effects and that the persistent elevation of hippocampal CREB may be associated with memory consolidation, these findings suggest that D_3 receptor-regulated CREB signaling in the hippocampus may be involved in these age-associated cognitive alterations (Xing et al., 2010b). In contrast, the D_3 receptor KO mice were impaired or showed no difference compared to the WT mice in spatial working memory (Chourbaji et al., 2008; Glickstein et al., 2002). Of note, spatial working memory was partially rescued by a D_1 receptor agonist, which caused a parallel increase in neuronal DRD3 Ser9Gly l c-*fos* expression in the PFC (Glickstein et al., 2002). This indicates that this cognitive task is partially dependent on optimal functioning of the D1R (Millan et al., 2010; Watson et al., 2012a).

In summary, D_3 receptor KO mice showed better performance than WT mice in measures of selective attention (mainly olfactory), aversive/associative learning, spatial memory and executive function (cognitive flexibility) independent of age. In addition, D_3 receptor antagonists enhanced the cognitive performance of the WT mice and did not affect the cognitive performance of the D_3 receptor KO mice, supporting the finding from pharmacological interventions that D_3 receptor blockade enhances cognitive function.

9. Implications for dopamine D_3 receptor antagonists as pro-cognitive agents

Deficits across multiple cognitive domains are common in neuropsychiatric disorders (Millan et al., 2012), contributing to worse clinical outcomes, social dysfunction, poorer QOL and greater caregivers' burden (Demirtas-Tatlidede et al., 2013). Despite this impact, the cognitive enhancing effects of currently available treatments are limited. Various pro-cognitive drug candidates, including AZD3480 (Velligan et al., 2012), dimebon (Morozova et al., 2012), EVP-6124 (Prickaerts et al., 2012), rimonabant (Boggs et al., 2012), rosiglitazone (Yi et al., 2012) and TC-5619 (Lieberman et al., 2013), have been investigated in clinical trials for neuropsychiatric disorders; however, most of them have failed to show clinically relevant effects. Thus, there is an urgent need to identify new therapeutic strategies that target cognitive dysfunction. There is great heterogeneity in the pathological mechanisms underlying symptom expression in neuropsychiatric disorders. Even within the same condition, subtypes present symptomatically different with regard to the presence and severity of psychosis, mood, anxiety, and cognitive impairment (e.g. schizophrenia spectrum disorders), depending on individual host factors and age of illness onset (Millan et al., 2012). Likewise, cognitive dysfunction is common to different neuropsychiatric disorders, suggesting that treatment interventions aimed at specific targets may be effective for cognitive dysfunction common across the different disorders (Millan et al., 2012).

As described in the present review, D_3 receptor antagonists hold promise as pro-cognitive drugs across a variety of cognitive domains, and are particularly attractive for age-related cognitive dysfunction, due to the improved side effect profile over traditional DA antagonists, which are associated with extrapyramidal symptoms, tardive dyskinesia, and

metabolic effects (Millan and Brocco, 2008). Selective D_3 receptor antagonists were not associated with catalepsy (Millan et al., 1995, 2000; Reavill et al., 2000) and were shown to counteract this effect of haloperidol in rodents (Gyertyan and Saghy, 2007). Thus, unlike most dopamine blocking agents, selective D_3 receptor antagonists do not appear to be associated with negative/cognitive symptoms and may also treat these adverse effects attributable to antipsychotics (Gross and Drescher, 2012).

This review has to be considered in light of the limitations within the literature. First, this review only focuses on the relationship between D_3 receptors and cognition. Many other mechanisms, from receptors to complex networks, should be taken into consideration when exploring cognitive treatments for neuropsychiatric disorders, assuming the possibility that some cognitive domains may be related to D_3 receptor signaling, while others may not, such as exploratory abilities and hippocampus-dependent spatial learning (Xing et al., 2010a; Zhu et al., 2010). Thus, D_3 receptor antagonists should also be studied as adjuncts to other cognitive treatments. Second, few studies have specifically addressed the relationship between D_3 receptors and cognition in humans. Most of the studies referred to in this review were animal studies that used cognitive modeling procedures, which may not reflect human cognition. Further, few animal models of cognitive dysfunction in the context of neuropsychopathology exist compared with those available for normal cognition. This hampers direct translation from animal models to real world clinical settings. Third, the results obtained from D_3 receptor KO mice may be due to the effects of a lack of D_3 receptors on adaptive developmental processes (Glickstein et al., 2005). Fourth, although D_3 receptor antagonists are promising as pro-cognitive drugs, few data have been published on the effects of selective D_3 receptor antagonists on cognitive dysfunction in humans. This is likely due to the lack of selective D_3 receptor antagonists available on the market.

In conclusion, human studies indicate that a relationship exists between D_3 receptors and cognitive dysfunction in individuals with neuropsychiatric disorders. Preclinical studies suggest that D_3 receptor antagonists may improve cognitive performance by enhancing the release of ACh in the PFC, disinhibiting the activity of DA neurons projecting to the NAc or PFC, or activating CREB signaling in the hippocampus. Given that currently available treatments have limited value for the management of cognitive dysfunction, D_3 receptor antagonists are worthy candidates for the enhancement of cognitive function in individuals with neuropsychiatric disorders. Clinical trials are needed to confirm their effects.

Acknowledgments

We sincerely appreciate Ms. Wanna Mar for her continuous support.

Role of the funding source

These grants had no further roles in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

Backman L, Nyberg L, Lindenberger U, Li SC, Farde L. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci Biobehav Rev. 2006; 30:791–807. [PubMed: 16901542]

Ball D, Hill L, Eley TC, Chorney MJ, Chorney K, Thompson LA, Detterman DK, Benbow C, Lubinski D, Owen M, McGuffin P, Plomin R. Dopamine markers and general cognitive ability. Neuroreport. 1998; 9:347–349. [PubMed: 9507981]

Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011; 377:1019–1031. [PubMed: 21371747]

Banasikowski TJ, Bespalov A, Drescher K, Behl B, Unger L, Haupt A, Schoemaker H, Sullivan JP, Gross G, Beninger RJ. Double dissociation of the effects of haloperidol and the dopamine D3 receptor antagonist ABT-127 on acquisition vs. expression of cocaine-conditioned activity in rats. J Pharmacol Exp Ther. 2010; 335:506–515. [PubMed: 20724485]

Basile M, Lin R, Kabbani N, Karpa K, Kilimann M, Simpson I, Kester M. Paralemmin interacts with D3 dopamine receptors: implications for membrane localization and cAMP signaling. Arch Biochem Biophys. 2006; 446:60–68. [PubMed: 16386234]

Baunez C, Robbins TW. Effects of dopamine depletion of the dorsal striatum and further interaction with subthalamic nucleus lesions in an attentional task in the rat. Neuroscience. 1999; 92:1343–1356. [PubMed: 10426489]

Bernaerts P, Tirelli E. Facilitatory effect of the dopamine D4 receptor agonist PD168,077 on memory consolidation of an inhibitory avoidance learned response in C57BL/6J mice. Behav Brain Res. 2003; 142:41–52. [PubMed: 12798264]

Bezard E, Ferry S, Mach U, Stark H, Leriche L, Boraud T, Gross C, Sokoloff P. Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. Nat Med. 2003; 9:762–767. [PubMed: 12740572]

Bhathena A, Wang Y, Kraft J, Idler K, Abel S, Holley-Shanks R, Robieson W, Spear B, Redden L, Katz D. Association between dopamine D3 receptor genotype and response to dopamine D3 receptor antagonist in schizophrenic subjects. Clin Pharmacol Ther. 2011; 89 (Suppl 1):S76.

Black KJ, Hershey T, Koller JM, Videen TO, Mintun MA, Price JL, Perlmutter JS. A possible substrate for dopamine-related changes in mood and behavior: prefrontal and limbic effects of a D3-preferring dopamine agonist. Proc Natl Acad Sci USA. 2002; 99:17113–17118. [PubMed: 12482941]

Boggs DL, Kelly DL, McMahon RP, Gold JM, Gorelick DA, Linthicum J, Conley RR, Liu F, Waltz J, Huestis MA, Buchanan RW. Rimonabant for neurocognition in schizophrenia: a 16-week double blind randomized placebo controlled trial. Schizophr Res. 2012; 134:207–210. [PubMed: 22137462]

Boileau I, Payer D, Houle S, Behzadi A, Rusjan PM, Tong J, Wilkins D, Selby P, George TP, Zack M, Furukawa Y, McCluskey T, Wilson AA, Kish SJ. Higher binding of the dopamine D3 receptor-preferring ligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin in methamphetamine polydrug users: a positron emission tomography study. J Neurosci. 2012; 32:1353–1359. [PubMed: 22279219]

Boileau I, Guttman M, Rusjan P, Adams JR, Houle S, Tong J, Hornykiewicz O, Furukawa Y, Wilson AA, Kapur S, Kish SJ. Decreased binding of the D3 dopamine receptor-preferring ligand [11C]-(+)-PHNO in drug-naive Parkinson's disease. Brain. 2009; 132:1366–1375. [PubMed: 19153147]

Bombin I, Arango C, Mayoral M, Castro-Fornieles J, Gonzalez-Pinto A, Gonzalez-Gomez C, Moreno D, Parellada M, Baeza I, Graell M, Otero S, Saiz PA, Patino-Garcia A. DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. Am J Med Genet B: Neuropsychiatr Genet. 2008; 147B:873–879. [PubMed: 18351593]

Boulougouris V, Castañé A, Robbins TW. Dopamine D2/D3 receptor agonist quinpirole impairs spatial reversal learning in rats: investigation of D3 receptor involvement in persistent behavior. Psychopharmacology (Berlin). 2009; 202:611–620. [PubMed: 18836703]

Boussaoud D, Kermadi I. The primate striatum: neuronal activity in relation to spatial attention versus motor preparation. Eur J Neurosci. 1997; 9:2152–2168. [PubMed: 9421175]

Bouthenet ML, Souil E, Martres MP, Sokoloff P, Giros B, Schwartz JC. Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D2 receptor mRNA. Brain Res. 1991; 564:203–219. [PubMed: 1839781]

Braszko JJ. Participation of D 1-4 dopamine receptors in the pro-cognitive effects of angiotensin IV and des-Phe 6 angiotensin IV. Neurosci Biobehav Rev. 2010; 34:343–350. [PubMed: 19686774]

Brusa L, Tiraboschi P, Koch G, Peppe A, Pierantozzi M, Ruggieri S, Stanzione P. Pergolide effect on cognitive functions in early-mild Parkinson's disease. J Neural Transm. 2005; 112:231–237. [PubMed: 15365788]

Brusa L, Bassi A, Stefani A, Pierantozzi M, Peppe A, Caramia MD, Boffa L, Ruggieri S, Stanzione P. Pramipexole in comparison to l-dopa: a neuropsychological study. J Neural Transm. 2003; 110:373–380. [PubMed: 12658365]

Bunten S, Happe S. Rotigotine transdermal system: a short review. Neuropsychiatr Dis Treat. 2006; 2:421–426. [PubMed: 19412491]

Burdick KE, Braga RJ, Nnadi CU, Shaya Y, Stearns WH, Malhotra AK. Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. J Clin Psychiatry. 2012; 73:103–112. [PubMed: 22152405]

Castorina A, Leggio GM, Giunta S, Magro G, Scapagnini G, Drago F, D'Agata V. Neurofibromin and amyloid precursor protein expression in dopamine D3 receptor knock-out mice brains. Neurochem Res. 2011; 36:426–434. [PubMed: 21170735]

Chiaroni P, Azorin JM, Dassa D, Henry JM, Giudicelli S, Malthiery Y, Planells R. Possible involvement of the dopamine D3 receptor locus in subtypes of bipolar affective disorder. Psychiatr Genet. 2000; 10:43–49. [PubMed: 10909128]

Chourbaji S, Brandwein C, Vogt MA, Dormann C, Mueller R, Drescher KU, Gross G, Gass P. Dopamine receptor 3 (D3) knockout mice show regular emotional behaviour. Pharmacol Res. 2008; 58:302–307. [PubMed: 18832038]

Cole DM, Beckmann CF, Searle GE, Plisson C, Tziortzi AC, Nichols TE, Gunn RN, Matthews PM, Rabiner EA, Beaver JD. Orbitofrontal connectivity with resting-state networks is associated with midbrain dopamine D3 receptor availability. Cereb Cortex. 2011; 22:2784–2793. [PubMed: 22186675]

Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2012; 69:e113–e125.

Cools R, Altamirano L, D'Esposito M. Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia. 2006; 44:1663–1673. [PubMed: 16730032]

Cosentino M, Colombo C, Mauri M, Ferrari M, Corbetta S, Marino F, Bono G, Lecchini S. Expression of apoptosis-related proteins and of mRNA for dopaminergic receptors in peripheral blood mononuclear cells from patients with Alzheimer disease. Alzheimer Dis Assoc Disord. 2009; 23:88–90. [PubMed: 19266703]

Costa A, Peppe A, Dell'Agnello G, Caltagirone C, Carlesimo GA. Dopamine and cognitive functioning in de novo subjects with Parkinson's disease: effects of pramipexole and pergolide on working memory. Neuropsychologia. 2009; 47:1374–1381. [PubMed: 19428401]

Czermak C, Wallner SJ, Kresse A, Schauer S, Aigner R, Hoefler G, Lehofer M, Liebmann PM. Baseline plasma epinephrine levels predict Wisconsin Card Sorting Test scores in healthy volunteers. Psychoneuroendocrinology. 2009; 34:625–628. [PubMed: 19041186]

de Krom M, Staal WG, Ophoff RA, Hendriks J, Buitelaar J, Franke B, de Jonge MV, Bolton P, Collier D, Curran S, van Engeland H, van Ree JM. A common variant in DRD3 receptor is associated with autism spectrum disorder. Biol Psychiatry. 2009; 65:625–630. [PubMed: 19058789]

Demirtas-Tatlidede A, Vahabzadeh-Hagh A, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology. 2012; 64:566–578. [PubMed: 22749945]

Diaz J, Pilon C, Le Foll B, Gros C, Triller A, Schwartz JC, Sokoloff P. Dopamine D3 receptors expressed by all mesencephalic dopamine neurons. J Neurosci. 2000; 20:8677–8684. [PubMed: 11102473]

Diaz J, Levesque D, Lammers CH, Griffon N, Martres MP, Schwartz JC, Sokoloff P. Phenotypical characterization of neurons expressing the dopamine D3 receptor in the rat brain. Neuroscience. 1995; 65:731–745. [PubMed: 7609872]

Donarum EA, Halperin RF, Stephan DA, Narayanan V. Cognitive dysfunction in NF1 knock-out mice may result from altered vesicular trafficking of APP/DRD3 complex. BMC Neurosci. 2006; 7:22. [PubMed: 16524466]

Dubertret C, Gorwood P, Ades J, Feingold J, Schwartz JC, Sokoloff P. Meta-analysis of DRD3 gene and schizophrenia: ethnic heterogeneity and significant association in Caucasians. Am J Med Genet. 1998; 81:318–322. [PubMed: 9674978]

El-Ghundi M, O'Dowd BF, George SR. Insights into the role of dopamine receptor systems in learning and memory. Rev Neurosci. 2007; 18:37–66. [PubMed: 17405450]

Ersche KD, Roiser JP, Lucas M, Domenici E, Robbins TW, Bullmore ET. Peripheral biomarkers of cognitive response to dopamine receptor agonist treatment. Psychopharmacology (Berlin). 2011; 214:779–789. [PubMed: 21088959]

Floresco SB, Magyar O. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berlin). 2006; 188:567–585. [PubMed: 16670842]

Fujisawa S, Buzsaki G. A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. Neuron. 2011; 72:153–165. [PubMed: 21982376]

Gross G, Drescher K. The role of dopamine D(3) receptors in antipsychotic activity and cognitive functions. Handb Exp Pharmacol. 2012; 213:167–210.

Glickstein SB, Desteno DA, Hof PR, Schmauss C. Mice lacking dopamine D2 and D3 receptors exhibit differential activation of prefrontal cortical neurons during tasks requiring attention. Cereb Cortex. 2005; 15:1016–1024. [PubMed: 15537671]

Glickstein SB, Hof PR, Schmauss C. Mice lacking dopamine D2 and D3 receptors have spatial working memory deficits. J Neurosci. 2002; 22:5619–5629. [PubMed: 12097513]

Gobert A, Di Cara B, Cistarelli L, Millan MJ. Piribedil enhances frontocortical and hippocampal release of acetylcholine in freely moving rats by blockade of alpha 2A-adrenoceptors: a dialysis comparison to talipexole and quinelorane in the absence of acetylcholinesterase inhibitors. J Pharmacol Exp Ther. 2003; 305:338–346. [PubMed: 12649387]

Gobert A, Lejeune F, Rivet JM, Cistarelli L, Millan MJ. Dopamine D3 (auto) receptors inhibit dopamine release in the frontal cortex of freely moving rats in vivo. J Neurochem. 1996; 66:2209–2212. [PubMed: 8780056]

Gobert A, Rivet JM, Audinot V, Cistarelli L, Spedding M, Vian J, Peglion JL, Millan MJ. Functional correlates of dopamine D3 receptor activation in the rat in vivo and their modulation by the selective antagonist, (+)-S 14297: II. Both D2 and "silent" D3 autoreceptors control synthesis and release in mesolimbic, mesocortical and nigrostriatal pathways. J Pharmacol Exp Ther. 1995; 275:899–913. [PubMed: 7473181]

Gong P, Zhang F, Lei X, Wu X, Chen D, Zhang W, Zhang K, Zheng A, Gao X. No observable relationship between the 12 genes of nervous system and reasoning skill in a young Chinese Han population. Cell Mol Neurobiol. 2011; 31:519–526. [PubMed: 21234799]

Graff-Guerrero A, Mizrahi R, Agid O, Marcon H, Barsoum P, Rusjan P, Wilson AA, Zipursky R, Kapur S. The dopamine D2 receptors in high-affinity state and D3 receptors in schizophrenia: a clinical [11C]-(+)-PHNO PET study. Neuropsychopharmacology. 2009; 34:1078–1086. [PubMed: 18987627]

Green MF. Stimulating the development of drug treatments to improve cognition in schizophrenia. Annu Rev Clin Psychol. 2007; 3:159–180. [PubMed: 17716052]

Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004; 72:41–51. [PubMed: 15531406]

Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull. 2000; 26:119–136. [PubMed: 10755673]

Gross G, Wicke K, Drescher KU. Dopamine D(3) receptor antagonism—still a therapeutic option for the treatment of schizophrenia. Naunyn Schmiedeberg's Arch Pharmacol. 2013; 386:155–166. [PubMed: 23128852]

Gross G, Drescher K. The role of dopamine D(3) receptors in antipsychotic activity and cognitive functions. Handb Exp Pharmacol. 2012:167–210.

Gupta S, Bousman CA, Chana G, Cherner M, Heaton RK, Deutsch R, Ellis RJ, Grant I, Everall IP. Dopamine receptor D3 genetic polymorphism (rs6280TC) is associated with rates of cognitive impairment in methamphetamine-dependent men with HIV: preliminary findings. J Neurovirol. 2011; 17:239–247. [PubMed: 21491142]

Gurevich EV, Joyce JN. Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. Neuropsychopharmacology. 1999; 20:60–80. [PubMed: 9885786]

Gurevich EV, Bordelon Y, Shapiro RM, Arnold SE, Gur RE, Joyce JN. Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia. A postmortem study. Arch Gen Psychiatry. 1997; 54:225–232. [PubMed: 9075463]

Gyertyan I, Saghy K, Laszy J, Elekes O, Kedves R, Gemesi LI, Pasztor G, Zajer-Balazs M, Kapas M, Agai Csongor E, Domany G, Kiss B, Szombathelyi Z. Subnanomolar dopamine D3 receptor antagonism coupled to moderate D2 affinity results in favourable antipsychotic-like activity in rodent models: II. Behavioural characterisation of RG-15 Naunyn Schmiedeberg's. Arch Pharmacol. 2008; 378:529–539.

Gyertyan I, Saghy K. The selective dopamine D3 receptor antagonists, SB 277011-A and S 33084 block haloperidol-induced catalepsy in rats. Eur J Pharmacol. 2007; 572:171–174. [PubMed: 17628535]

Hall H, Halldin C, Dijkstra D, Wikstrom H, Wise LD, Pugsley TA, Sokoloff P, Pauli S, Farde L, Sedvall G. Autoradiographic localisation of D3-dopamine receptors in the human brain using the selective D3-dopamine receptor agonist (+)-[3H]PD 128907. Psychopharmacology (Berlin). 1996; 128:240–247. [PubMed: 8972543]

Hale MW, Crowe SF. The effects of selective dopamine agonists on a passive avoidance learning task in the day-old chick. Behav Pharmacol. 2002; 13:295–301. [PubMed: 12218510]

Hamidovic A, Kang UJ, de Wit H. Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. J Clin Psychopharmacol. 2008; 28:45–51. [PubMed: 18204340]

Heidbreder C. Rationale in support of the use of selective dopamine D(3) receptor antagonists for the pharmacotherapeutic management of substance use disorders. Naunyn Schmiedeberg's Arch Pharmacol. 2013; 386:167–176. [PubMed: 23104235]

Heidbreder CA, Newman AH. Current perspectives on selective dopamine D(3) receptor antagonists as pharmacotherapeutics for addictions and related disorders. Ann N Y Acad Sci. 2010; 1187:4–34. [PubMed: 20201845]

Heidbreder CA, Gardner EL, Xi ZX, Thanos PK, Mugnaini M, Hagan JJ, Ashby CR Jr. The role of central dopamine D3 receptors in drug addiction: a review of pharmacological evidence. Brain Res Brain Res Rev. 2005; 49:77–105. [PubMed: 15960988]

Hubble JP. Pre-clinical studies of pramipexole: clinical relevance. Eur J Neurol. 2000; 7 (Suppl 1):15–20. [PubMed: 11054154]

Ilani T, Ben-Shachar D, Strous RD, Mazor M, Sheinkman A, Kotler M, Fuchs S. A peripheral marker for schizophrenia: increased levels of D3 dopamine receptor mRNA in blood lymphocytes. Proc Natl Acad Sci USA. 2001; 98:625–628. [PubMed: 11149951]

Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G, Sokoloff P. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. Proc Natl Acad Sci USA. 2006; 103:10753–10758. [PubMed: 16809426]

Joseph JD, Wang YM, Miles PR, Budygin EA, Picetti R, Gainetdinov RR, Caron MG, Wightman RM. Dopamine autoreceptor regulation of release and uptake in mouse brain slices in the absence of D(3) receptors. Neuroscience. 2002w; 112:39–49. [PubMed: 12044470]

Joyce JN, Millan MJ. Dopamine D3 receptor antagonists as therapeutic agents. Drug Discov Today. 2005; 10:917–925. [PubMed: 15993811]

Joyce JN. Dopamine D3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. Pharmacol Ther. 2001; 90:231–259. [PubMed: 11578658]

Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. Br Med J. 2005; 331:321–327. [PubMed: 16081444]

Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. Handb Exp Pharmacol. 2012; 213:11–37.

Keri S, Juhasz A, Rimanoczy A, Szekeres G, Kelemen O, Cimmer C, Szendi I, Benedek G, Janka Z. Habit learning and the genetics of the dopamine D3 receptor: evidence from patients with schizophrenia and healthy controls. Behav Neurosci. 2005; 119:687–693. [PubMed: 15998189]

Khaled MA, Farid Araki K, Li B, Coen KM, Marinelli PW, Varga J, Gaal J, Le Foll B. The selective dopamine D3 receptor antagonist SB 277011-A, but not the partial agonist BP 897, blocks cue-induced reinstatement of nicotine-seeking. Int J Neuropsychopharmacol. 2010; 13:181–190. [PubMed: 19995481]

Khan ZU, Gutierrez A, Martin R, Penafiel A, Rivera A, De La Calle A. Differential regional and cellular distribution of dopamine D2-like receptors: an immunocytochemical study of subtype-specific antibodies in rat and human brain. J Comp Neurol. 1998; 402:353–371. [PubMed: 9853904]

Kim B, Choi EY, Kim CY, Song K, Joo YH. Could HTR2A T102C and DRD3 Ser9Gly predict clinical improvement in patients with acutely exacerbated schizophrenia? Results from treatment responses to risperidone in a naturalistic setting. Hum Psychopharmacol. 2008; 23:61–67. [PubMed: 17924589]

Koeltzow TE, Xu M, Cooper DC, Hu XT, Tonegawa S, Wolf ME, White FJ. Alterations in dopamine release but not dopamine autoreceptor function in dopamine D3 receptor mutant mice. J Neurosci. 1998; 18:2231–2238. [PubMed: 9482807]

Kumar U, Patel SC. Immunohistochemical localization of dopamine receptor subtypes (D1R-D5R) in Alzheimer's disease brain. Brain Res. 2007; 1131:187–196. [PubMed: 17182012]

Lacroix LP, Ceolin L, Zocchi A, Varnier G, Garzotti M, Curcuruto O, Heidbreder CA. Selective dopamine D3 receptor antagonists enhance cortical acetylcholine levels measured with high-performance liquid chromatography/tandem mass spectrometry without anti-cholinesterases. J Neurosci Methods. 2006; 157:25–31. [PubMed: 16697046]

Lacroix LP, Hows ME, Shah AJ, Hagan JJ, Heidbreder CA. Selective antagonism at dopamine D3 receptors enhances monoaminergic and cholinergic neurotransmission in the rat anterior cingulate cortex. Neuropsychopharmacology. 2003; 28:839–849. [PubMed: 12637956]

Lane HY, Liu YC, Huang CL, Hsieh CL, Chang YL, Chang L, Chang YC, Chang WH. Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. J Psychiatry Neurosci. 2008; 33:47–53. [PubMed: 18197272]

Laszy J, Laszlovszky I, Gyertyan I. Dopamine D3 receptor antagonists improve the learning performance in memory-impaired rats. Psychopharmacology (Berlin). 2005; 179:567–575. [PubMed: 15619116]

Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P. Genetics of dopamine receptors and drug addiction: a comprehensive review. Behav Pharmacol. 2009; 20:1–17. [PubMed: 19179847]

Le Foll B, Diaz J, Sokoloff P. Neuroadaptations to hyperdopaminergia in dopamine D3 receptor-deficient mice. Life Sci. 2005a; 76:1281–1296. [PubMed: 15642598]

Le Foll B, Goldberg SR, Sokoloff P. The dopamine D3 receptor and drug dependence: effects on reward or beyond? Neuropharmacology. 2005b; 49:525–541. [PubMed: 15963538]

Le Foll B, Schwartz JC, Sokoloff P. Disruption of nicotine conditioning by dopamine D(3) receptor ligands. Mol Psychiatry. 2003; 8:225–230. [PubMed: 12610655]

Le Foll B, Frances H, Diaz J, Schwartz JC, Sokoloff P. Role of the dopamine D3 receptor in reactivity to cocaine-associated cues in mice. Eur J Neurosci. 2002; 15:2016–2026. [PubMed: 12099907]

Lee B, Butcher GQ, Hoyt KR, Impey S, Obrietan K. Activity-dependent neuroprotection and cAMP response element-binding protein (CREB): kinase coupling, stimulus intensity, and temporal regulation of CREB phosphorylation at serine 133. J Neurosci. 2005; 25:1137–1148. [PubMed: 15689550]

Levant B. Differential distribution of D3 dopamine receptors in the brains of several mammalian species. Brain Res. 1998; 800:269–274. [PubMed: 9685676]

Levesque D, Diaz J, Pilon C, Martres MP, Giros B, Souil E, Schott D, Morgat JL, Schwartz JC, Sokoloff P. Identification, characterization, and localization of the dopamine D3 receptor in rat brain using 7-[3H]hydroxy-N,N-di-*n*-propyl-2-aminotetralin. Proc Natl Acad Sci USA. 1992; 89:8155–8159. [PubMed: 1518841]

Lieberman JA, Dunbar G, Segreti AC, Girgis RR, Seoane F, Beaver JS, Duan N, Hosford DA. A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. Neuropsychopharmacology. 2013; 38:968–975. [PubMed: 23303043]

Limosin F, Romo L, Batel P, Ades J, Boni C, Gorwood P. Association between dopamine receptor D3 gene BalI polymorphism and cognitive impulsiveness in alcohol-dependent men. Eur Psychiatry. 2005; 20:304–306. [PubMed: 15935433]

Loiseau F, Millan MJ. Blockade of dopamine D(3) receptors in frontal cortex, but not in sub-cortical structures, enhances social recognition in rats: similar actions of D(1) receptor agonists, but not of D(2) antagonists. Eur Neuropsychopharmacol. 2009; 19:23–33. [PubMed: 18793829]

Lundstrom K, Turpin MP, Large C, Robertson G, Thomas P, Lewell XQ. Mapping of dopamine D3 receptor binding site by pharmacological characterization of mutants expressed in CHO cells with the Semliki Forest virus system. J Recept Signal Transduct Res. 1998; 18:133–150. [PubMed: 9651882]

Lundstrom K, Turpin MP. Proposed schizophrenia-related gene polymorphism: expression of the Ser9Gly mutant human dopamine D3 receptor with the Semliki Forest virus system. Biochem Biophys Res Commun. 1996; 225:1068–1072. [PubMed: 8780735]

Marcellino D, Ferre S, Casado V, Cortes A, Le Foll B, Mazzola C, Drago F, Saur O, Stark H, Soriano A, Barnes C, Goldberg SR, Lluis C, Fuxe K, Franco R. Identification of dopamine D1-D3 receptor heteromers. Indications for a role of synergistic D1–D3 receptor interactions in the striatum. J Biol Chem. 2008; 283:26016–26025. [PubMed: 18644790]

Marcondes MC, Flynn C, Watry DD, Zandonatti M, Fox HS. Methamphetamine increases brain viral load and activates natural killer cells in simian immunodeficiency virus-infected monkeys. Am J Pathol. 2010; 177:355–361. [PubMed: 20489154]

McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006:19.

Micale V, Cristino L, Tamburella A, Petrosino S, Leggio GM, Di Marzo V, Drago F. Enhanced cognitive performance of dopamine D3 receptor “knock-out” mice in the step-through passive-avoidance test: assessing the role of the endocannabinoid/endovanilloid systems. Pharmacol Res. 2010; 61:531–536. [PubMed: 20149873]

Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, Connor R, Davis S, Deakin B, DeRubeis RJ, Dubois B, Geyer MA, Goodwin GM, Gorwood P, Jay TM, Joels M, Mansuy IM, Meyer-Lindenberg A, Murphy D, Rolls E, Saletu B, Spedding M, Sweeney J, Whittington M, Young LJ. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov. 2012; 11:141–168. [PubMed: 22293568]

Millan MJ, Buccafusco JJ, Loiseau F, Watson DJ, Decamp E, Fone KC, Thomasson-Perret N, Hill M, Mocaer E, Schneider JS. The dopamine D3 receptor antagonist, S33138, counters cognitive impairment in a range of rodent and primate procedures. Int J Neuropsychopharmacol. 2010; 13:1035–1051. [PubMed: 20663270]

Millan MJ, Brocco M. Cognitive impairment in schizophrenia: a review of developmental and genetic models, and pro-cognitive profile of the optimised D(3)4D(2) antagonist, S33138. Therapie. 2008; 63:187–229. [PubMed: 18718210]

Millan MJ, Svenningsson P, Ashby CR Jr, Hill M, Egeland M, Dekeyne A, Brocco M, Di Cara B, Lejeune F, Thomasson N, Munoz C, Mocaer E, Crossman A, Cistarelli L, Girardon S, Iob L, Veiga S, Gobert A. S33138 [N-[4-[2-[(3aS,9bR)-8-cyano-1,3a,4,9b-tetrahydro[1]-benzopyrano[3,4-c] pyrrol-2(3H)-yl)-ethyl]phenylacetamide], a preferential dopamine D3 versus D2 receptor antagonist and potential antipsychotic agent. II A neurochemical, electrophysiological and behavioral characterization in vivo. J Pharmacol Exp Ther. 2008; 324:600–611. [PubMed: 18024787]

Millan MJ, Di Cara B, Dekeyne A, Panayi F, De Groote L, Sicard D, Cistarelli L, Billiras R, Gobert A. Selective blockade of dopamine D(3) versus D(2) receptors enhances frontocortical cholinergic transmission and social memory in rats: a parallel neurochemical and behavioural analysis. J Neurochem. 2007; 100:1047–1061. [PubMed: 17266737]

Millan MJ, Dekeyne A, Rivet JM, Dubuffet T, Lavielle G, Brocco M. S33084, a novel, potent, selective, and competitive antagonist at dopamine D(3)-receptors: II. Functional and behavioral

profile compared with GR218,231 and L741,626. J Pharmacol Exp Ther. 2000; 293:1063–1073. [PubMed: 10869411]

Millan MJ, Peglion JL, Vian J, Rivet JM, Brocco M, Gobert A, Newman-Tancredi A, Dacquet C, Bervoets K, Girardon S. Functional correlates of dopamine D3 receptor activation in the rat in vivo and their modulation by the selective antagonist, (+)-S 14297: 1. Activation of postsynaptic D3 receptors mediates hypothermia, whereas blockade of D2 receptors elicits prolactin secretion and catalepsy. J Pharmacol Exp Ther. 1995; 275:885–898. [PubMed: 7473180]

Mizrahi R, Agid O, Borlido C, Suridjan I, Rusjan P, Houle S, Remington G, Wilson AA, Kapur S. Effects of anti-psychotics on D3 receptors: a clinical PET study in first episode antipsychotic naive patients with schizophrenia using [11C]-(+)-PHNO. Schizophr Res. 2011; 131:63–68. [PubMed: 21684721]

Morissette M, Goulet M, Grondin R, Blanchet P, Bedard PJ, Di Paolo T, Levesque D. Associative and limbic regions of monkey striatum express high levels of dopamine D3 receptors: effects of MPTP and dopamine agonist replacement therapies. Eur J Neurosci. 1998; 10:2565–2573. [PubMed: 9767387]

Morozova MA, Beniashvili AG, Lepilkina TA, Rupchev GE. Double-blind placebo-controlled randomized efficacy and safety trial of add-on treatment of dimebon plus risperidone in schizophrenic patients during transition from acute psychotic episode to remission. Psychiatr Danub. 2012; 24:159–166. [PubMed: 22706414]

Mugnaini M, Iavarone L, Cavallini P, Griffante C, Oliosi B, Savoia C, Beaver J, Rabiner EA, Micheli F, Heidbreder C, Andorn A, Merlo Pich E, Bani M. Occupancy of brain dopamine D3 receptors and drug craving: a translational approach. Neuropsychopharmacology. 2013; 38:302–312. [PubMed: 22968817]

Murray AM, Ryoo HL, Gurevich E, Joyce JN. Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. Proc Natl Acad Sci USA. 1994; 91:11271–11275. [PubMed: 7972046]

Murray AM, Ryoo H, Joyce JN. Visualization of dopamine D3-like receptors in human brain with [125I]epidepride. Eur J Pharmacol. 1992; 227:443–445. [PubMed: 1359976]

Nissbrandt H, Ekman A, Eriksson E, Heilig M. Dopamine D3 receptor antisense influences dopamine synthesis in rat brain. Neuroreport. 1995; 6:573–576. [PubMed: 7766866]

Perio A, Terranova JP, Worms P, Bluthe RM, Dantzer R, Biziere K. Specific modulation of social memory in rats by cholinomimetic and nootropic drugs, by benzodiazepine inverse agonists, but not by psychostimulants. Psychopharmacology (Berlin). 1989; 97:262–268. [PubMed: 2567026]

Pieramico V, Esposito R, Sensi F, Cilli F, Mantini D, Mattei PA, Frazzini V, Ciavardelli D, Gatta V, Ferretti A, Romani GL, Sensi SL. Combination training in aging individuals modifies functional connectivity and cognition, and is potentially affected by dopamine-related genes. PLoS One. 2012; 7:e43901. [PubMed: 22937122]

Piggott MA, Marshall EF, Thomas N, Lloyd S, Court JA, Jaros E, Burn D, Johnson M, Perry RH, McKeith IG, Ballard C, Perry EK. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. Brain. 1999; 122 (Pt. 8):1449–1468. [PubMed: 10430831]

Prickaerts J, van Goethem NP, Chesworth R, Shapiro G, Boess FG, Methfessel C, Reneerkens OA, Flood DG, Hilt D, Gawryl M, Bertrand S, Bertrand D, Konig G. EVP-6124, a novel and selective alpha7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of alpha7 nicotinic acetylcholine receptors. Neuropharmacology. 2012; 62:1099–1110. [PubMed: 22085888]

Pugsley TA, Davis MD, Akunne HC, MacKenzie RG, Shih YH, Damsma G, Wikstrom H, Whetzel SZ, Georgic LM, Cooke LW, et al. Neurochemical and functional characterization of the preferentially selective dopamine D3 agonist PD 128907. J Pharmacol Exp Ther. 1995; 275:1355–1366. [PubMed: 8531103]

Rabiner EA, Slifstein M, Nobrega J, Plisson C, Huiban M, Raymond R, Diwan M, Wilson AA, McCormick P, Gentile G, Gunn RN, Laruelle MA. In vivo quantification of regional dopamine-D3 receptor binding potential of (+)-PHNO: studies in non-human primates and transgenic mice. Synapse. 2009; 63:782–793. [PubMed: 19489048]

Reavill C, Taylor SG, Wood MD, Ashmeade T, Austin NE, Avenell KY, Boyfield I, Branch CL, Cilia J, Coldwell MC, Hadley MS, Hunter AJ, Jeffrey P, Jewitt F, Johnson CN, Jones DN, Medhurst AD, Middlemiss DN, Nash DJ, Riley GJ, Routledge C, Stemp G, Thewlis KM, Trail B, Vong AK, Hagan JJ. Pharmacological actions of a novel, high-affinity, and selective human dopamine D(3) receptor antagonist, SB-277011-A. J Pharmacol Exp Ther. 2000; 294:1154–1165. [PubMed: 10945872]

Rektorova I, Rektor I, Bares M, Dostal V, Ehler E, Fanfrdlova Z, Fiedler J, Klajblova H, Kulist'ak P, Ressner P, Svatova J, Urbanek K, Veliskova J. Cognitive performance in people with Parkinson's disease and mild or moderate depression: effects of dopamine agonists in an add-on to L-dopa therapy. Eur J Neurol. 2005; 12:9–15. [PubMed: 15613141]

Richtand NM, Woods SC, Berger SP, Strakowski SM. D3 dopamine receptor, behavioral sensitization, and psychosis. Neurosci Biobehav Rev. 2001; 25:427–443. [PubMed: 11566480]

Richtand NM, Kelsoe JR, Segal DS, Kuczenski R. Regional quantification of D1, D2, and D3 dopamine receptor mRNA in rat brain using a ribonuclease protection assay. Brain Res Mol Brain Res. 1995; 33:97–103. [PubMed: 8774950]

Rybakowski JK, Borkowska A, Czerski PM, Kapelski P, Dmitrzak-Weglarz M, Hauser J. An association study of dopamine receptors polymorphisms and the Wisconsin Card Sorting Test in schizophrenia. J Neural Transm. 2005; 112:1575–1582. [PubMed: 15785860]

Saddichha S, Pandey V. Alzheimer's and non-alzheimer's dementia: a critical review of pharmacological and nonpharmacological strategies. Am J Alzheimers Dis Other Demen. 2008; 23:150–161. [PubMed: 18332476]

Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM. Comparison of pramipexole with and without domperidone co-administration on alertness, autonomic, and endocrine functions in healthy volunteers. Br J Clin Pharmacol. 2007; 64:591–602. [PubMed: 17578485]

Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM. Comparison of pramipexole and amisulpride on alertness, autonomic and endocrine functions in healthy volunteers. Psychopharmacology (Berlin). 2006a; 187:498–510. [PubMed: 16802163]

Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM. Comparison of pramipexole and modafinil on arousal, autonomic, and endocrine functions in healthy volunteers. J Psychopharmacol. 2006b; 20:756–770. [PubMed: 16401653]

Sanford M, Scott LJ. Rotigotine transdermal patch: a review of its use in the treatment of Parkinson's disease. CNS Drugs. 2011; 25:699–719. [PubMed: 21790211]

Scheller D, Ullmer C, Berkels R, Gwarek M, Lubbert H. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. Naunyn Schmiedeberg's Arch Pharmacol. 2009; 379:73–86. [PubMed: 18704368]

Schotte A, Janssen PF, Bonaventure P, Leysen JE. Endogenous dopamine limits the binding of antipsychotic drugs to D3 receptors in the rat brain: a quantitative autoradiographic study. Histochem J. 1996; 28:791–799. [PubMed: 8968731]

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007; 27:2349–2356. [PubMed: 17329432]

Serretti A, Macciardi F, Cusin C, Lattuada E, Souery D, Lipp O, Mahieu B, Van Broeckhoven C, Blackwood D, Muir W, Aschauer HN, Heiden AM, Ackenheil M, Fuchshuber S, Raeymaekers P, Verheyen G, Kaneva R, Jablensky A, Papadimitriou GN, Dikeos DG, Stefanis CN, Smeraldi E, Mendlewicz J. Linkage of mood disorders with D2, D3 and TH genes: a multicenter study. J Affect Disord. 2000; 58:51–61. [PubMed: 10760558]

Sesack SR, Grace AA. Cortico-basal ganglia reward network: microcircuitry. Neuropsychopharmacology. 2010; 35:27–47. [PubMed: 19675534]

Sigala S, Missale C, Spano P. Opposite effects of dopamine D2 and D3 receptors on learning and memory in the rat. Eur J Pharmacol. 1997; 336:107–112. [PubMed: 9384221]

Smith AG, Neill JC, Costall B. The dopamine D3/D2 receptor agonist 7-OH-DPAT induces cognitive impairment in the marmoset. Pharmacol Biochem Behav. 1999; 63:201–211. [PubMed: 10371648]

Soffie M, Bronchart M. Age-related scopolamine effects on social and individual behaviour in rats. Psychopharmacology (Berlin). 1988; 95:344–350. [PubMed: 3137620]

Sokoloff P, Leriche L, Diaz J, Louvel J, Pumain R. Direct and indirect interactions of the dopamine D(3) receptor with glutamate pathways: implications for the treatment of schizophrenia. Naunyn Schmiedeberg's Arch Pharmacol. 2013; 386:107–124. [PubMed: 23001156]

Sokoloff P, Diaz J, Le Foll B, Guillin O, Leriche L, Bezard E, Gross C. The dopamine D3 receptor: a therapeutic target for the treatment of neuropsychiatric disorders. CNS Neurol Disord Drug Targets. 2006; 5:25–43. [PubMed: 16613552]

Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature. 1990; 347:146–151. [PubMed: 1975644]

Stanwood GD, Artymyshyn RP, Kung MP, Kung HF, Lucki I, McGonigle P. Quantitative autoradiographic mapping of rat brain dopamine D3 binding with [(125)I]7-OH-PIPAT: evidence for the presence of D3 receptors on dopaminergic and non-dopaminergic cell bodies and terminals. J Pharmacol Exp Ther. 2000; 295:1223–1231. [PubMed: 11082459]

Stragier B, Demaegdt H, De Bundel D, Smolders I, Sarre S, Vauquelin G, Ebinger G, Michotte Y, Vanderheyden P. Involvement of insulin-regulated aminopeptidase and/or aminopeptidase N in the angiotensin IV-induced effect on dopamine release in the striatum of the rat. Brain Res. 2007; 1131:97–105. [PubMed: 17169335]

Suzuki M, Hurd YL, Sokoloff P, Schwartz JC, Sedvall G. D3 dopamine receptor mRNA is widely expressed in the human brain. Brain Res. 1998; 779:58–74. [PubMed: 9473588]

Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012; 11:697–707. [PubMed: 22814541]

Swant J, Stramiello M, Wagner JJ. Postsynaptic dopamine D3 receptor modulation of evoked IPSCs via GABA (A) receptor endocytosis in rat hippocampus. Hippocampus. 2008; 18:492–502. [PubMed: 18240318]

Szekeres G, Keri S, Juhasz A, Rimanoczy A, Szendi I, Czimmer C, Janka Z. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B: Neuropsychiatr Genet. 2004; 124B:1–5. [PubMed: 14681904]

Takahashi H, Yamada M, Suhara T. Functional significance of central D1 receptors in cognition: beyond working memory. J Cereb Blood Flow Metab. 2012; 32:1248–1258. [PubMed: 22234338]

Taubenfeld SM, Wiig KA, Bear MF, Alberini CM. A molecular correlate of memory and amnesia in the hippocampus. Nat Neurosci. 1999; 2:309–310. [PubMed: 10204535]

Tregellas JR, Tanabe J, Rojas DC, Shatti S, Olincy A, Johnson L, Martin LF, Soti F, Kem WR, Leonard S, Freedman R. Effects of an alpha 7-nicotinic agonist on default network activity in schizophrenia. Biol Psychiatry. 2011; 69:7–11. [PubMed: 20728875]

Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, Honczarenko K, Dioszeghy P, Hill D, Anderson T, Myllyla V, Kassubek J, Steiger M, Zucconi M, Tolosa E, Poewe W, Surmann E, Whitesides J, Boroojerdi B, Chaudhuri KR. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord. 2011; 26:90–99. [PubMed: 21322021]

Ukai M, Tanaka T, Kameyama T. Effects of the dopamine D3 receptor agonist, R(+)-7-hydroxy-N,N-di-n-propyl-2-aminote-tralin, on memory processes in mice. Eur J Pharmacol. 1997; 324:147–151. [PubMed: 9145765]

Vanhauwe JF, Josson K, Luyten WH, Driessen AJ, Leysen JE. G-protein sensitivity of ligand binding to human dopamine D (2) and D(3) receptors expressed in *Escherichia coli*: clues for a constrained D(3) receptor structure. J Pharmacol Exp Ther. 2000; 295:274–283. [PubMed: 10991990]

Velligan D, Brenner R, Sicuro F, Walling D, Riesenberg R, Sfera A, Merideth C, Sweitzer D, Jaeger J. Assessment of the effects of AZD3480 on cognitive function in patients with schizophrenia. Schizophr Res. 2012; 134:59–64. [PubMed: 22088556]

Walton M, Woodgate AM, Muravlev A, Xu R, During MJ, Dragunow M. CREB phosphorylation promotes nerve cell survival. J Neurochem. 1999; 73:1836–1842. [PubMed: 10537041]

Watson DJ, Loiseau F, Ingallinesi M, Millan MJ, Marsden CA, Fone KC. Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: a key role for the prefrontal cortex. Neuropsychopharmacology. 2012a; 37:770–786. [PubMed: 22030711]

Watson DJ, Marsden CA, Millan MJ, Fone KC. Blockade of dopamine D but not D receptors reverses the novel object discrimination impairment produced by post-weaning social isolation: implications for schizophrenia and its treatment. Int J Neuropsychopharmacol. 2012b; 15:471–484. [PubMed: 21414250]

Wilson AA, McCormick P, Kapur S, Willeit M, Garcia A, Hussey D, Houle S, Seeman P, Ginovart N. Radio-synthesis and evaluation of [11C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol as a potential radiotracer for in vivo imaging of the dopamine D2 high-affinity state with positron emission tomography. J Med Chem. 2005; 48:4153–4160. [PubMed: 15943487]

Winslow JT, Camacho F. Cholinergic modulation of a decrement in social investigation following repeated contacts between mice. Psychopharmacology (Berlin). 1995; 121:164–172. [PubMed: 8545521]

Xing B, Kong H, Meng X, Wei SG, Xu M, Li SB. Dopamine D1 but not D3 receptor is critical for spatial learning and related signaling in the hippocampus. Neuroscience. 2010a; 169:1511–1519. [PubMed: 20600656]

Xing B, Meng X, Wei S, Li S. Influence of dopamine D3 receptor knockout on age-related decline of spatial memory. Neurosci Lett. 2010b; 481:149–153. [PubMed: 20600590]

Yi Z, Fan X, Wang J, Liu D, Freudenreich O, Goff D, Henderson DC. Rosiglitazone and cognitive function in clozapine-treated patients with schizophrenia: a pilot study. Psychiatry Res. 2012:79–82.

Zagmutt FJ, Tarrants ML. Indirect comparisons of adverse events and dropout rates in early Parkinson's disease trials of pramipexole, ropinirole, and rasagiline. Int J Neurosci. 2012; 122:345–353. [PubMed: 22304415]

Zhu X, Li T, Peng S, Ma X, Chen X, Zhang X. Maternal deprivation-caused behavioral abnormalities in adult rats relate to a non-methylation-regulated D2 receptor levels in the nucleus accumbens. Behav Brain Res. 2010; 209:281–288. [PubMed: 20144661]

Table 1

Pharmacological dopamine D3 receptor intervention and cognition in animals.

Procedure	Perturbation	Drugs	Effect on D3R	Species	Effects	Principle cognitive domain	References
Social recognition	Delay (2 h)	S33084, S33138, SB-277011, (+)S14297	Antagonist	Rat	Improvement of deficit	Mainly olfactory, memory (delay) and attention (scopolamine)	Millan et al. (2007, 2008), Millan and Brocco (2008), Loiseau and Millan (2009)
	Scopolamine	S33084, S33138, SB-277011, (+)S14297	Antagonist	Rat	Improvement of deficit		Millan et al. (2007, 2008), Millan and Brocco (2008)
	None	S33084, SB-277011	Antagonist	Rat	No effect		Millan et al. (2007), Watson et al. (2012a)
	None	PD128907, 7-OH-DPAT	Agonist	Rat	Impairment		Millan et al. (2007), Watson et al. (2012a)
Social discrimination	Delay (30 min)	S33084, S33138	Antagonist	Rat	Improvement of deficit	Selective attention (mainly olfactory)	Millan et al. (2010), Watson et al. (2012a
5-Choice serial reaction time	None	S33138	Antagonist	Rat	No effect	Attention (accuracy), speed of processing (latency)	Millan et al. (2008), Millan and Brocco (2008)
Passive avoidance	Scopolamine	S33138, Nefadotride	Antagonist	Mouse, rat	Improvement of deficit	Aversive/associative learning	Sigala et al. (1997), Millan et al. (2008), Millan and Brocco (2008)
	Dizocilipine	S33138	Antagonist	Mouse	Improvement of deficit		Millan et al. (2008), Millan and Brocco (2008)

Procedure	Perturbation	Drugs	Effect on D3R	Species	Effects	Principle cognitive domain	References
	Delay (3 h)	7-OH-DPAT	Agonist	Chick	Impairment		Hale and Crowe (2002)
	Delay (3 h)	U-99194+7-OH-DPAT	Antagonist+agonist	Chick	No effect		Hale and Crowe (2002)
	None	S33138	Antagonist	Rat	No effect		Millan et al. (2008), Millan and Brocco (2008)
	None	U-99194A	Antagonist	Mouse	Enhancement		Bernaerts and Tirelli (2003)
	None	7-OH-DPAT	Agonist	Mouse	Impairment		Ukai (1997), Bernaerts and Tirelli (2003)
Object recognition	Isolation rearing	S33084, S33138	Antagonist	Rat	Improvement of deficit	Visual, declarative memory, attention	Watson et al. (2012b)
	Delay (4 h)	S33084, S33138	Antagonist	Rat	Improvement of deficit		Millan et al. (2010), Watson et al. (2012a)
	Delay (2 min)	PD128907	Agonist	Rat	Impairment		Watson et al. (2012a)
	Delay (2 min)	S33084+PD128907	Antagonist+agonist	Rat	No effect		Watson et al. (2012a)
Variable delayed response	Chronic, low-dose MPTP	S33138	Antagonist	Rhesus monkey	Improvement of deficit with short delays	Attention (short delays), spatial working memory (long delays)	Millan et al. (2010)
Attentional set shifting	Chronic, low-dose MPTP	S33138	Antagonist	Rhesus monkey	Improvement of deficit	Executive function (cognitive flexibility)	Millan et al. (2010)
Spatial discrimination and serial reversal learning	None	Nefadotride	Antagonist	Rat	No effect	Spatial reversal learning	Boulougouris et al. (2009)
Delayed matching to sample	Aging (27 years)	S33138	Antagonist	Rhesus monkey	Improvement of deficit with long delays	Visual working memory, attention	Millan et al. (2010)
Reversal visual object discrimination	None	7-OH-DPAT	Agonist	Marmoset	Impairment	Reversal object learning	Smith et al. (1999)
Water labyrinth	FG-7142	BP-897	Partial agonist	Rat	Improvement of deficit	Spatial learning	Laszy et al. (2005)

Eur Neuropsychopharmacol. Author manuscript; available in PMC 2013 August 20.

Procedure	Perturbation	Drugs	Effect on D3R	Species	Effects	Principle cognitive domain	References
	Scopolamine	BP-897	Partial agonist	Rat	No effect		Laszy et al. (2005)
	FG-7142	SB277011, RGH-1756, U-99194A	Antagonist	Rat	Improvement of deficit		Laszy et al. (2005)
	Scopolamine/diazepam	SB277011, RGH-1756, U-99194A, RG-15	Antagonist	Rat	Improvement of deficit		Laszy et al. (2005), Gyertyan et al. (2008)

Abbreviations: D3R=dopamine D3 receptor.

Eur Neuropsychopharmacol. Author manuscript; available in PMC 2013 August 20.

Table 2

Genetic dopamine D3 receptor intervention (D3R knockout) and cognition in animals.

Procedure	Perturbation	Mice	Drug	Effects	Principle cognitive domain	References
Social discrimination	Delay (1/2 h)	D3R KO	None	Enhancement	Selective attention (mainly olfactory)	Watson et al. (2012a)
	Delay (1/2 h)	D3R KO	S33084 (D3R antagonist)	No effect		Watson et al. (2012a)
	Delay (1/2 h)	WT	S33084 (D3R antagonist)	Improvement		Watson et al. (2012a)
Passive avoidance	None	D3R KO	None	Improvement	Aversive/associative learning	Micale et al. (2010)
Attentional set shifting	None	D3R KO	None	Enhancement	Executive function (cognitive flexibility)	Glickstein et al. 2005
T-maze	None	D3R KO	None	No effect	Spatial working memory	Chourbaji et al. (2008)
Delayed alternation	None	D3R KO	None	Impairment		Glickstein et al. 2002
Morris water maze	Aging	D3R KO	None	Enhancement		Xing et al. (2010a, 2010b)

Abbreviations: D3R=dopamine D3 receptor, KO=knockout, WT=wild type.