European Neuropsychopharmacology (2013) 23, 799–813

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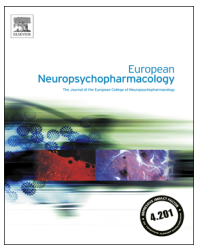

REVIEW

The potential role of dopamine D_3 receptor neurotransmission in cognition

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Received 11 March 2013; received in revised form 22 May 2013; accepted 24 May 2013

KEYWORDS
Dopamine D3 receptor;
Cognition;
Dopamine D3 receptor antagonist

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 cognition using PubMed, MEDLINE and EMBASE. The search terms included "dopamine D_3 receptor"

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0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2013.05.006

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.

Contents

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 $\alpha4\beta2$ central neuronal nicotinic receptor agonist) (Velligan et al., 2012), dimebon (a serotonin 5HT-6 receptor antagonist) (Morozova et al., 2012), EVP-6124, TC-5619 ($\alpha7$ 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