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The triple monoaminergic reuptake inhibitor DOV 216,303 has antidepressant effects in the rat olfactory bulbectomy model and lacks sexual side effects

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Received 6 May 2008; received in revised form 1 July 2008; accepted 29 July 2008

KEYWORDS

Depression;
TUI;
Sexual behavior;
Olfactory bulbectomy;
Antidepressant;
Rats

Abstract

Current antidepressants have a delayed onset of action and disturbing side effects, including inhibition of sexual behavior. It is hypothesized that novel drugs, hitting multiple disease-relevant targets, may yield a new generation of superior antidepressants. One such approach is simultaneous inhibition of serotonin, norepinephrine and dopamine transporters. We tested the triple uptake inhibitor (TUI), DOV 216,303 (5, 10 and 20 mg/kg) after 1, 7 and 14 days administration in the olfactory bulbectomized (OBX) rat depression model, and in a model of rat sexual behavior to detect putative sexual side effects. Chronic, but not acute treatment of DOV 216,303 (20 mg/kg) normalized OBX-induced hyperactivity in the open field, similar to the effect of imipramine (20 mg/kg). None of the doses of DOV 216,303 had any effect on sexual behavior at any time point. The results indicate that DOV 216,303 displays antidepressant efficacy and is devoid of sexual side effects.

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1. Introduction

Depression is a severe psychiatric disorder with lifetime prevalence as high as 20%. The World Health Organization says it will be the second largest global burden of disease (DALYs) by the year 2020, illustrating the severity and impact of the disorder (Manji et al., 2001; Nestler et al., 2002). Depression is not a unitary disorder and most experts agree that it should be considered a syndrome (DSM-IV 2000) comprised of a spectrum of various symptoms, making animal research into the underlying mechanisms difficult but feasible (Berton and Nestler, 2006).

The first effective treatments for depression were primarily monoamine modulating drugs (Klerman and Cole, 1967). Over the past five decades, the leading theory behind the mechanism of action of these drugs has been known as the monoamine hypothesis of depression, postulating that depressive symptoms are primarily caused by disruptions in serotonin, noradrenaline and/or dopamine neurotransmission (Schechter et al., 2005). This hypothesis was based on findings that monoamine oxidase inhibitors and tricyclic antidepressants elevated monoamine levels in the central nervous system, and appeared to have antidepressant efficacy (Eriksson, 2000). The next generations of antidepressants, selective serotonin reuptake inhibitors and selective serotonin/norepinephrine reuptake inhibitors, were variations on this monoamine theme. Blockade of noradrenaline or dopamine also appeared to have antidepressant effects (Stahl et al., 2004), suggesting that compounds blocking all three monoamine transporters would constitute effective antidepressants.

The involvement of dopamine in depression is thought to be dependent upon dopaminergic reward mechanisms in the limbic system (Lemke et al., 2005). Several animal studies have shown that dopamine neurons in the ventral tegmental area (VTA) play a role in movement abnormalities associated with Parkinson's disease (PD), and neural projections from the VTA to the frontal lobes may play a role in decreased initiative (Brown and Gershon, 1993). Also, homovanillic acid (the major metabolite of dopamine) has been shown to be decreased in the cerebrospinal fluid of depressed patients (Gershon et al., 2007), and hypofunction of the mesolimbic dopamine pathways is thought to be a mediator of anhedonia, a major symptom of depression (Willner, 1983). Dopamine also plays a role in sexual behavior, and is thought to mediate ejaculation, although this may be dependant upon specific dopamine receptor sub-types (Peeters and Giuliano, 2007).

Recently, the development of triple monoamine uptake inhibitors (TUIs) has piqued the interest of various pharmaceutical and biotech companies. SSRIs exert sexually inhibitory effects, but only after chronic treatment (Mos et al., 1999; Waldinger et al., 2002; De Jong et al., 2005b). Adding a stimulatory dopaminergic component to a dual serotonin-noradrenaline reuptake inhibitor might compensate for the inhibitory action of chronic serotonin transporter inhibition on sexual behavior without losing the antidepressant efficacy. It has previously been suggested that treatment with dopaminergic agonists may decrease SSRI induced sexual dysfunction (Fava and Rankin, 2002). It has been previously shown that patients treated with SSRIs showed sexual improvements when also treated with bupropion, a

norepinephrine/dopamine reuptake inhibitor (Gitlin et al., 2002). Addition of a dopaminergic component to the proven antidepressant profile of combined 5-HT and NA inhibitor uptake might have advantages. Clinical and pre-clinical evidence links one of the core symptoms of depression (anhedonia) to deficits in dopaminergic transmission (D'Aquila et al., 2004; Naranjo et al., 2001; Willner et al., 2005; Nestler and Carlezon, 2006), and that dopaminergic stimulation may be associated with pro-sexual effects (Hull et al., 2004).

Removal of the olfactory bulbs (OBX) in rats results in similarities to brain chemistry seen in depressed humans (Song and Leonard, 2005; Slotkin et al., 2005), such as altered dopamine (Masini et al., 2004) and serotonin concentrations in the brain (Van der Stelt et al., 2005). Olfactory bulb ablation also leads to enlarged lateral and 3rd ventricles, as well as decreased hippocampal volume, phenomena that are also observed in depressed humans (Sheline, 2003). Bulb ablation also results in several behavioral changes, including increased hyperactivity in a novel environment (Breuer et al., 2007), and deficits in passive-avoidance learning and anhedonia (Wieronska et al., 2001). Olfactory bulbectomy is one of the best available models to predict antidepressant activity, as OBX-induced depressive symptoms respond to chronic, but not acute, antidepressant treatment (Grecksch et al., 1997; Uzunova et al., 2004; Song and Leonard, 2005).

The present study investigates the behavioral effects of the TUI DOV 216,303 ([(+/-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride]) (Skolnick et al., 2003, 2006) in the OBX depression model, and in sexual behavior in endophenotypically normal rats (Olivier et al., 2006; Pattij et al., 2005). It should be noted that two different rat strains were used for this experiment, due to the fact that the bulk of sexual behavior studies has been done using Wistar rats (Olivier et al., 2006; Chan et al., 2007), while most bulbectomy studies have been performed using the Sprague-Dawley strain (Kelly et al., 1997; Song and Leonard, 2005; Breuer et al., 2007).

DOV 216,303 inhibits NE, 5-HT and DA reuptake in vitro at 20, 14 and 78 nM, respectively (Skolnick et al., 2003, 2006) and is active in acute antidepressant tests like the forced swim and the tail suspension (Skolnick et al., 2003, 2006). DOV 216,303 is also well-tolerated in humans, and significantly reduced the HAM-D scores of depressed patients, similar to citalopram (Skolnick et al., 2006). The goal of this study was to compare the effects of DOV 216,303 in these two animal models reflecting antidepressant activity and sexual side effects, creating an opportunity to predict human therapeutic efficacy and sexual side effects of this putative new antidepressant.

2. Materials and methods

2.1. Experiment I: olfactory bulbectomy

2.1.1. Animals

One hundred-and-twenty male albino Sprague-Dawley rats (Harlan, Zeist, The Netherlands) weighing between 220 and 250 g were housed four/cage on a 12 h: 12 h light dark cycle, with lights off at 18:00 and on at 6:00. Food and water were

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