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The triple reuptake inhibitor DOV 216,303 induces long-lasting enhancement of brain reward activity as measured by intracranial self-stimulation in rats

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ABSTRACT

Triple reuptake inhibitors (TRIs) are potential new antidepressants, which not only enhance brain serotonin and norepinephrine concentrations but also increase dopamine levels. Therefore TRIs are believed to have faster therapeutic onset than SSRIs, and may be particularly useful for the treatment of anhedonia (i.e. inability to experience pleasure), one of the core symptoms of major depression. The current study aimed at getting better insight into the rewarding properties of DOV 216,303, which is a TRI, regarding its possible use to treat anhedonia. It is known that psychostimulant drugs lower intracranial self-stimulation (ICSS) reward thresholds, reflecting enhanced brain reward activity, whereas withdrawal from those compounds mostly results in increased ICSS thresholds. Therefore we assessed the effects of DOV 216,303 on ICSS thresholds in rats. Animals were trained in the discrete-trial current-threshold procedure and after stable ICSS reward thresholds were established, animals received one injection per day of DOV 216,303 (20 mg/kg) or amphetamine (5 mg/kg) for four consecutive days. ICSS thresholds were assessed 3, 6, and 23 h after each injection. DOV 216,303 decreased ICSS thresholds up to 6 h after drug treatment. To our knowledge this is the first time that a triple reuptake inhibitor, DOV 216,303, induces relatively long-lasting enhancement of brain reward activity. Elevated ICSS thresholds were found after amphetamine administration, which is consistent with previously reported reward deficits induced after amphetamine-withdrawal.

1. Introduction

Pharmacological treatment of Major Depressive Disorder is mainly based on increasing serotonin and/or norepinephrine levels by selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs) or dual acting drugs, acting on both serotonin and norepinephrine (SNRIs). Nevertheless, it takes a relatively long time before the therapeutic effects of SSRIs are established. Moreover, anhedonia (one of the core symptoms of Major Depression), which is defined as the inability to experience pleasure, is often not alleviated with currently available antidepressants.

A role for dopamine in the pathophysiology of depression has been postulated and extensively reviewed (Dunlop and Nemeroff, 2007; Kapur and Mann, 1992; Naranjo et al., 2001; Nestler and Carlezon, 2006). Evidence for disturbed dopaminergic reward function in depression comes from preclinical research in which the dopamine response after palatable food is blunted in the chronic mild stress animal model for depression (Di Chiara et al., 1999). Moreover, clinical research also demonstrated a role for a dysfunctional reward system in depression (Tremblay et al., 2002, 2005).

Co-targeting of the dopaminergic system has been proven to be effective in antidepressant treatment. Bupropion, which is a dopamine reuptake inhibitor (DRI) and NRI, augments antidepressant treatment with SSRIs (Trivedi et al., 2006). Moreover, bupropion alone shows antidepressant effects (Dhillon et al., 2008) and even enhances brain reward function in rats (Cryan et al., 2003a). Furthermore, the D_2/D_3 receptor agonist pramipexole has antidepressant-like effects in an animal model of depression (Breuer et al., 2009) and can also augment the effects of SSRI-based antidepressants (Goldberg et al., 2004; Gupta et al., 2006).

These insights have led to the development of triple reuptake inhibitors (TRIs). TRIs are considered as a new class of antidepressants (Guiard et al., 2009; Marks et al., 2008b; Millan, 2009; Skolnick and Basile, 2007). DOV 216,303 is such a TRI, which

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enhances brain serotonin, norepinephrinergic and dopaminergic neurotransmission (Prins et al., 2010; 2011; Skolnick et al., 2006). By impacting dopaminergic neurotransmission, TRIs are believed to have faster therapeutic onset than SSRIs (Willner, 1997) and may be particularly useful for the treatment of anhedonia (Marks et al., 2008a).

The current study aimed at getting better insight into the rewarding properties of DOV 216,303. In this study only one dose of DOV 216,303 (20 mg/kg, p.o.) was used which had shown to have a clear monoamine release profile, including an increase in dopaminergic neurotransmission, even after repeated administration (Prins et al., 2010, 2011). A similar monoamine release profile has been observed after DOV 216,303 (20 mg/kg, i.p.). To assess the potential of DOV 216,303 to activate brain reward systems we examined the effects of acute, sub-chronic and after cessation of treatment with DOV 216,303 and amphetamine on intracranial self stimulation (ICSS) thresholds in rats. ICSS is considered as a direct measure of brain reward (Carlezon and Chartoff, 2007; Kenny, 2007; Markou and Koob, 1992).

The hypothesis of the current study is that DOV 216,303, which is also known to increase dopaminergic neurotransmission, increases brain reward functioning as reflected by decreasing intracranial self stimulation (ICSS) thresholds.

2. Material and methods

2.1. Animals

Twenty-four male Wistar rats (Harlan, Horst, the Netherlands) weighing between 290–350 g at the time of surgery were socially housed, four per cage on a 12 h light-dark cycle with lights on at 6:00 h and off at 18:00 h. Food and water were available ad libitum, except for the first 3 days of ICSS training where animals were given 20 g food per animals per day in order to have a more optimized training of the animals (Carr, 1990). All animal experimental procedures were carried out in accordance with the government guidelines and approved by the Ethical Committee for Animal Research at Utrecht University, the Netherlands.

2.2. Surgery

Animals were anesthetized by inhalation of isoflurane gas (2–3%), mixed with nitrous oxide and oxygen and placed in a stereotaxic instrument (Kopf, David Kopf Instruments). Lidocaine hydrochloride (2%)+adrenaline (0.001%) were applied in the incision as local anesthetic. Bipolar ICSS electrodes (cut to a length of 11 mm) were implanted into the lateral hypothalamus (LH). The coordinates of the LH were AP: −0.5 mm from bregma; ML: ±1.7 mm from bregma; DV: −8.3 mm from dura. The incisor bar was adjusted to 5 mm above the interaural line (Pellegrino et al., 1979). Electrodes were anchored with four screws and dental acrylic on the skull. All animals received Rimadyl (5 mg/kg, subcutaneously) for pain relief twice daily, up to a total of four injections.

2.3. ICSS apparatus

All ICSS experiments were performed in eight sound-attenuating operant chambers (30.5 × 30 × 17 cm) with a grid floor and a wheel manipulandum in one of the sides. The implanted electrode was connected to the electrical stimulator through a swivel and a bipolar connector cable (Plastics One), ensuring unrestrained movement throughout the ICSS procedure. The electrical stimulations were delivered by a constant current stimulator (Med Associates Inc.). The stimulator was connected to a computer running MED-PC IV (Med Associates, Inc.) controlling all stimulation settings, programs and recording of data.

2.4. ICSS procedure

In order for the animals to make the association that turning the wheel results in electrical stimulation, all animals were initially trained to turn the wheel manipulandum on a fixed ratio 1 schedule of reinforcement. In this training phase each quarter turn of the wheel resulted in an electrical stimulus with train duration of 500 ms. After several successful training sessions (more than 1000 turnings in 30 min), the rats were trained on a discrete-trial current-threshold procedure according to the procedure described by Markou and Koob (1992). At the start of a trial rats received a free, non-contingent stimulus and had 7.5 s to react and turn the wheel a quarter turn to obtain a second, contingent stimulus (positive response) of the same current intensity and duration (100 ms). In case no response occurred during the 7.5 s period, a negative response was recorded. The 7.5 s period in which a positive or negative response occurred was followed by an inter trial interval (ITI) with a duration range from 7.5 to 12.5 s. Responses during the ITI resulted in a delay of onset of the next trial of 12.5 s. Turning the wheel in the 2 s after a positive response did not have further consequences. Responses during this period often reflect the force with which the animal turned the wheel, because a powerful pull will result in more than a quarter turn of the wheel. Animals were subjected to alternating descending and ascending series of current intensities starting with a descending series. The stimulus intensity of the first series was set 40 μA above each animal's own baseline. Current levels were presented in sets of five trials of the same current intensity and altered by steps of 5 μA.

2.5. Parameters

2.5.1. ICSS thresholds

The current threshold for a series was defined as the midpoint between two consecutive current intensities for which animals responded in at least three of the five trials and two consecutive current intensities for which animals did not respond in three or more of the five trials. The overall threshold of the session was defined as the mean of the thresholds of the four alternating descending and ascending series. Stable thresholds were defined as less than 10% change in threshold over three consecutive days after at least 10 days of testing.

2.5.2. Response latencies

The response latency is the time between the presentation of the non-contingent stimulus and the turning of the wheel by the animal. The overall response latencies were defined as the mean response latency of all trials during which a positive response occurred.

2.6. Drugs

Animals were divided into three treatment groups. Treatment groups consisted of vehicle ($n=4$, sterile water, administered p.o. by oral gavage and $n=3$, 0.9% saline, administered i.p.), 5 mg/kg D-amphetamine (dissolved in 0.9% saline administered i.p. in a volume of 1 ml/kg, $n=6$), or 20 mg/kg DOV 216,303 [(+/−)-1-(3,4-dichlorophenyl)-3-azabicyclo-[3.1.0]hexane hydrochloride) synthesized by Sepracor Inc., Marlborough, USA], (dissolved in sterile water and administered p.o. in a volume of 2 ml/kg by oral gavage, $n=7$).