Two-Week Administration of the Combined Serotonin-Noradrenaline Reuptake Inhibitor Duloxetine Augments Functioning of Mesolimbic Incentive Processing Circuits

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Background: Anhedonia and lack of motivation are core symptoms of major depressive disorder (MDD). Neuroimaging studies in MDD patients have shown reductions in reward-related activity in terminal regions of the mesolimbic dopamine (DA) system, such as the ventral striatum. Monoamines have been implicated in both mesolimbic incentive processing and the mechanism of action of antidepressant drugs. However, not much is known about antidepressant effects on mesolimbic incentive processing in humans, which might be related to the effects on anhedonia.

Methods: To investigate the short-term effects of antidepressants on reward-related activity in the ventral striatum, we investigated the effect of the combined serotonin-norepinephrine reuptake inhibitor duloxetine. Healthy volunteers underwent functional magnetic resonance imaging in a randomized, double-blind, placebo-controlled, crossover study. After taking duloxetine (60 mg once a day) or placebo for 14 days, participants completed a monetary incentive delay task that activates the ventral striatum during reward anticipation.

Results: Our results ($n = 19$) show enhanced ventral striatal responses after duloxetine administration compared with placebo. Moreover, this increase in ventral striatal activity was positively correlated with duloxetine plasma levels.

Conclusions: This is the first study to demonstrate that antidepressants augment neural activity in mesolimbic DA incentive processing circuits in healthy volunteers. These effects are likely caused by the increase in monoamine neurotransmission in the ventral striatum. Our findings suggest that antidepressants may alleviate anhedonia by stimulating incentive processing.

Key Words: Duloxetine, functional magnetic resonance imaging (fMRI), monoamine, reward, serotonin-norepinephrine reuptake inhibitor, ventral striatum

Anhedonia, defined as reduced reactivity to pleasurable stimuli, and lack of motivation are core symptoms of major depressive disorder (MDD). Thus, MDD patients exhibit reduced responsiveness to rewards in behavioral tasks (1,2). Neuroimaging studies in MDD patients with anhedonia show that these changes in reward responsiveness may be a sign of dysregulations of neural activity in mesolimbic incentive processing circuits (3–10), of which the nucleus accumbens (NAcc) is a key component. Both affective state and anhedonia are influenced by antidepressants (11,12) and 1-week administration in healthy subjects increases the processing of positive affective information (13). Moreover, response to antidepressants appears to be positively related to rewarding experiences (14). Convergent evidence in rodents has shown that administration of antidepressants abolished depressive-like behavior and recovered motivated behaviors (15–17). Antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs) increase extracellular serotonin (5HT) and norepinephrine (NE) levels by inhibition of reuptake to the presynaptic sites. Furthermore, mesolimbic dopaminergic (DA) neurons projecting to the NAcc have been suggested to be involved in the therapeutic actions of some antidepressants (18,19), probably through 5HT modulation of DA function (20). A previous study by McCabe and colleagues (21) showed that the administration of a selective serotonin reuptake inhibitor decreased neural responses to appetitive stimuli in the ventral striatum, which includes the approximate location of the NAcc. However, a norepinephrine reuptake inhibitor did not suppress neural responses in this brain region. Nevertheless, these findings suggest that antidepressants may influence reward processes in mesolimbic incentive processing circuits.

Blood oxygenation level–dependent functional magnetic resonance imaging (BOLD-fMRI) techniques have been applied to investigate the neural mechanism of antidepressant treatment and their effects on brain activity. Most of these studies investigated their acute effects on brain function (22–25). However, antidepressant treatment in MDD patients appears to have a therapeutic effect after approximately 2 weeks of administration (26,27). We used fMRI to investigate the effects of 2-week administration of the SNRI duloxetine on reward-related neural activity in a within-subjects, placebo-controlled, crossover design. Such a design excludes interindividual variance when probing the drug effect, and incidental associations with nonobserved variables are easily eliminated. Thus, each subject underwent fMRI twice. To reduce task repetition effects, we carefully counterbalanced the order of drug conditions between subjects. Duloxetine was chosen because SNRIs have been suggested to affect symptoms to a larger extent than other antidepressants (28). Moreover, duloxetine is a dual-action antide-

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pressant and therefore has a broader pharmacological profile than single-action antidepressants (29). In the MRI scanner, healthy participants performed a modified version of the monetary incentive delay (MID) task during which they had to give an instrumental response to obtain a monetary reward. fMRI studies have demonstrated that BOLD responses in the ventral striatum are particularly strong during reward anticipation (30,31) and when instrumental responses are required to attain rewards (32). In addition, clinical reports of anhedonia are primarily associated with low levels of anticipation (33,34) and reduced ventral striatal reactivity to rewarding stimuli (4,5,35). Therefore, we hypothesized that ventral striatal responses to reward anticipation would be enhanced after 2-week administration of duloxetine.

Methods and Materials

Subjects

Twenty-six healthy subjects participated in this double-blind, placebo-controlled, crossover study and were recruited via advertisement and screened approximately 1 week before study entry. Two participants withdrew before scanning from the experiment because of side effects, and five subjects were excluded for technical failures. Therefore, 19 subjects (10 female) aged between 18 and 50 years (mean age: 24.6 $\pm$ 7.1 years) were included in our analysis. Before screening, we informed subjects about all procedures and risks before we asked them to sign an informed consent form. Afterward, subjects underwent a physical examination and a standardized evaluation of medical history. Current or lifetime psychiatric illnesses were assessed using the Mini International Neuropsychiatric Interview (36). To exclude subjects with clinically relevant depressive symptoms, they were screened using the Dutch version of the Beck Depression Inventory (37). All subjects had a total score below 10 (mean score 2.5 $\pm$ 3.4). Trait anxiety was measured using the Dutch version of the State-Trait Anxiety Inventory (38). Changes in mood state were measured by using the Dutch version of the Profile of Mood States (POMS) (39). Participants completed the POMS upon arrival and after magnetic resonance scanning during both drug conditions. Twelve-lead electrocardiogram was recorded. In addition, a venous blood sample was obtained at screening for analyzing general hematology and blood chemistry. Participants were excluded if they consumed psychotropic drugs within 2 months before the start of the trial. At screening and on each scanning day, a urine sample was collected and tested for psychotropic drug use. Female participants were tested for pregnancy before each drug supply using commercially available urine sticks and would have been excluded if they tested positive. Furthermore, no subjects had a known hypersensitivity to duloxetine or contraindications (hepatic impairment, severe renal impairment with a glomerular filtration rate $<$ 30 mL/min). Subjects with a history of prescribed medication, with the exception of oral contraceptives and paracetamol, within the month (or within 3 months if they participated in a medication study) before the start of this trial were not included. Other exclusion criteria were medically relevant abnormalities in any laboratory parameter, color blindness, electrocardiogram, or medical or surgical history that the investigator regarded as potentially affecting the outcome of the trial. All subjects had a body mass index between 18.5 and 25.0, good mental (36) and physical health as determined by medical history and examination, and no MRI contraindications. This study was approved by the local ethical review board (Commissie mensgebonden onderzoek [CMO] Region Arnhem-Nijmegen, the Netherlands), and all participants provided written informed consent.

Drug Intervention

After screening, we randomly assigned subjects to two groups: starting with either placebo or duloxetine. Medication was taken each morning as a capsule containing placebo or 60 mg duloxetine for 14 consecutive days. Treatment periods were separated by a washout period of at least 14 days (range: 14–42 days; mean $\pm$ SD: 20 $\pm$ 9 days). Thus, the trial lasted on average 8 weeks for each subject. Subjects underwent fMRI on the final day of each drug or placebo period (approximately 2 and 6 weeks after trial onset).

Analysis of Duloxetine Plasma Levels

To measure duloxetine levels, a 10-mL venous blood sample was collected in an ethylenediamine-tetraacetic acid anticoagulant tube on both scanning days to maintain double-blinding between 10:30 and 11 AM Within 30 min, the samples were centrifuged for 10 min at 3500 rpm at room temperature. The separated plasma was kept in a labeled plastic tube in the freezer at –20 C° until the end of the study.

High performance liquid chromatography (HPLC) was used to measure duloxetine levels (10–100 μg/L) with prothiaden (100 μg/L) as the internal standard. The high-performance liquid chromatography system delivered the mobile phase at a flow rate of 1.1 mL/min and an Inertsil ODS-3 5μ, 50 $\times$ 4.6 mm separation column, heated to 40°C.

Monetary Incentive Delay Task

This task was based on the MID task developed by Knutson *et al.* (30) and consisted of 25 potentially rewarding trials, 25 nonrewarding trials, and 25 periods of low-level fixation with an overall mean duration equal to trials. We used a modified version of this task because we aimed to shorten the experiment and were mainly interested in reward anticipation, which recruits the ventral striatum (30). In total, trials lasted between 8.5 and 11.5 sec (mean: 10 sec). Thus, the total duration of the task was 12.5 min. At the beginning of each trial a cue (cue duration: 3.5–8.5 sec; mean 6 sec) was presented signaling a potentially rewarding (red square) or nonrewarding (green square) trial. Following this cue, a target was presented to which subjects had to respond as fast as possible (by pressing a button) irrespective of the cue type. When the button was pushed within the presentation time of the circle, the target remained on the screen, thus providing the participant with feedback that the target was hit. Otherwise, it disappeared. When the target was hit in a rewarding trial, participants earned 1 euro. Although the presentation of immediate feedback makes it difficult to isolate outcome responses, it increases the power to detect anticipatory activity because it allows the use of shorter intertrial intervals. The success of this approach is reflected in robust main effects of reward anticipation (40,41) and the absence of session-repetition effects, which is critical for a crossover design as used here. After disappearance of the target (duration: 1.2–5.3 sec; mean 3.25 sec), short feedback (500 msec) on the cumulative gain was provided. To ascertain that reward outcome was similar across participants and sessions, the target duration was variable (150–500 msec) and shortened to 20 msec for the subsequent trial when the previous target was hit. The target duration was lengthened with 10 msec in the subsequent trial when the previous target was missed. This procedure results in a hit rate of about 33% on average, ensuring that all participants won approximately the same amount of money (between 8 and 11 euro). Because of this adaptive reinforcement schedule, no trials were excluded. Before the experiment, practice trials were presented inside the scanner to familiarize the participants with the task. Participants were instructed to hit the