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Zolpidem increases GABA in depressed volunteers maintained on SSRIs

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ABSTRACT

Individuals with major depressive disorder (MDD) often use hypnotics like zolpidem (Ambien®) to improve sleep in addition to their selective serotonin reuptake inhibitor (SSRI) regimen. SSRIs act in part to restore disrupted GABAergic activity, but benzodiazepines and related drugs have been shown to lower GABA in a way that may be counter to these therapeutic effects. The present within-subject, single-blind, placebo-controlled study measured changes in GABA in the anterior cingulate (ACC) and thalamus of volunteers maintained on SSRIs for the treatment of MDD ($n=14$) following zolpidem (10 mg) administration. In addition to neurochemical measurements obtained using proton magnetic resonance spectroscopy (^{1}H MRS) at 4 T, a series of questionnaires were administered to assess subjective effects associated with acute zolpidem exposure. Zolpidem elevated GABA levels in both voxels of interest ($P<0.05$) in the depressed participants, which could imply normalization, given the lower baseline levels associated with depression. The subjective drug experience in the depressed cohort was similar to that reported previously by healthy volunteers, and no relationships existed between GABA increases and the observed behavioral effects. Aside from treating insomnia, using zolpidem in the presence of SSRIs may have some unidentified therapeutic effects for depressed individuals.

1. Introduction

The GABAergic system has been implicated in the chemical imbalances underlying major depressive disorder (MDD; reviewed by Sanacora and Saricicek (2007), and studies using proton magnetic resonance spectroscopy (^{1}H MRS) have revealed reduced GABA in the brains of depressed individuals (Bhagwagar et al., 2008; Gabbay et al., 2012; Hasler et al., 2007; Kugaya et al., 2003; Price et al., 2009; Sanacora et al., 1999, 2004). Accordingly, antidepressant selective serotonin reuptake inhibitors (SSRIs) increase cortical GABA levels (Bhagwagar et al., 2004; Sanacora et al., 2002) in addition to their ability to increase serotonin (Fuller, 1994).

Upwards of one third of depressed people take prescription sleep-aids as well as their SSRI therapy (Thase, 2006). Several controlled trials have shown that combining benzodiazepine-like hypnotics with antidepressants improves disordered sleep in MDD (Asnis et al., 1999; Fava et al., 2006, 2011), although mood is not necessarily improved (Fava et al., 2011). In fact it has been suggested that benzodiazepines can cause or worsen depression (Hall and Zisook, 1981; Petty et al., 1995), and benzodiazepine-like hypnotics may cause unpleasant subjective effects (Licata et al., 2009). Interestingly, while benzodiazepines and related drugs are known to increase fast inhibitory neurotransmission (Perrais and Ropert, 1999), ^{1}H MRS has shown that they reduce GABA levels in some areas of the brain (Goddard et al., 2004; Licata et al., 2009). The implication is that this drug class could counter the restorative effects of SSRIs on dysfunctional GABA in MDD (Sanacora and Saricicek, 2007) and have functional significance in terms of mood states.

In the current study, ^{1}H MRS was employed to assess the effect of the hypnotic zolpidem (Ambien®; 10 mg) on GABA in volunteers maintained on stable SSRIs for the treatment of MDD. The study design was based on previous work in healthy volunteers showing a reduction in GABA following acute administration of zolpidem (Licata et al., 2009), and predicted that in addition to reduced GABA, self-reported subjective drug assessments administered periodically throughout the experimental session would reveal effects indicative of a negative mood state. Together these measures were aimed at understanding more about the neurobiological mechanisms that contribute to the behavioral effects of this popular hypnotic (Morlock et al., 2006), particularly in depressed individuals.

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[1] The experiments described herein complied with the current laws of the United States of America.

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2. Methods

2.1. Participants

Fourteen volunteers (4 male and 10 female) between the ages of 21–40 (mean ± standard deviation [SD] 29.6 ± 5.1 years) completed this study. Volunteers were recruited through advertisements from the Boston metropolitan area. This study was reviewed and approved by the McLean Hospital Institutional Review Board, and was in accord with the Helsinki Declaration. All volunteers provided informed consent and they were compensated for their participation.

Participants were required to meet DSM-IV-TR criteria for MDD, and to be maintained on stable citalopram (≤ 40 mg/day), fluoxetine (≤ 40 mg/day), paroxetine (≤ 40 mg/day), or sertraline (≤ 100 mg/day). Participants could not be taking any other psychotropic medications. They could not meet criteria for any other major psychiatric disorders including past or current substance abuse, have a history of neurological disorders, have any medical conditions, or be pregnant. Structural MRI scans were required to be normal. At the beginning of the study visit, participants provided urine and breath samples to be screened for drug and alcohol use, respectively. Female participants also underwent a urine pregnancy test.

2.2. Study design

Participants visited the laboratory once for this single-blind, placebo-controlled, double-scan study. Each ^{1}H MRS scanning session lasted approximately 1 h. Participants received a capsule containing placebo 45 min prior to the first scan, and an identical capsule containing zolpidem (10 mg) 45 min prior to the second scan. Data were acquired from two separate voxels of interest placed within the anterior cingulate (ACC) and thalamus. Throughout the 8-h experimental session participants provided self-reported ratings of mood and subjective drug effects at regular intervals. A standard breakfast was provided to help control the rate of drug absorption, and lunch was provided after the second scan. In addition to monetary compensation, round-trip taxicab transportation was provided for all participants on the study day.

2.3. Neuroimaging

All magnetic resonance data were collected on a 4.0 T Direct-Drive™ whole-body magnetic resonance scanner (Agilent Technologies; Palo Alto, CA). A volumetric quadrature, birdcage-design (Robarts Research; London, Canada) radio frequency head coil operating at 170.3 MHz was used for proton imaging and spectroscopy. Once participants were positioned inside the bore, scout images confirmed optimal positioning at the magnet's isocenter. The unsuppressed water signal was used to manually shim the global water signal. The transmitter was set back onto the water resonance, and a series of high-contrast T_1-weighted anatomical images were taken in the sagittal and axial planes with the following parameters: TE/TR = 6.2 s/11.4 ms, FOV = 22 × 22 × 8 cm (sagittal) and 22 × 22 × 16 cm (axial), readout duration = 4 ms, receive bandwidth = ± 32 kHz, in-plane matrix size = 128 × 256 × 16 (sagittal) and 256 × 256 × 64 (axial), in-plane resolution = 0.94 × 1.9 mm (sagittal) and 0.94 × 0.94 mm (axial), readout points = 512, slice thickness = 2.5 mm, flip-angle = 11°.

2.3.1. Proton MRS

The high-resolution anatomical images were used as a guide to place voxels in the dorsal ACC (3 × 2 × 2 cm) and left thalamic lobe (2 × 2 × 3 cm) as shown in Fig. 1. Proton spectroscopy implemented a MEGAPRESS sequence (Mescher et al., 1998) to obtain difference-edited GABA-optimized spectra and 68 ms single-echo spectra. Manual shimming of the magnetic field within the prescribed voxel was done with global water linewidths ranging from 9 to 12 Hz. Following the automated optimization of water suppression power and tip angles, the MEGAPRESS sequence was implemented with the following acquisition parameters: TR/TE = 2 s/68 ms, spectral bandwidth = 2 kHz, readout duration = 512 ms, NEX = 384, total scan duration = 13 min. MEGAPRESS spectra were acquired in bins of 16 averages each to ensure a full phase-cycle per bin and thus minimize external coherences corrupting the signal. A total of 24 such bins were collected for each voxel with the MEGAPRESS editing pulse frequency alternating between 1.89 ppm ("ON") and approximately 300 ppm off resonance ("OFF"), with the power of the MEGAPRESS editing pulses unaltered. Once the first dataset was collected from the ACC, a second set was collected from a voxel in the left thalamus.

2.3.2. Proton MRS processing

All spectroscopic data processing and analyses were undertaken on a LINUX workstation using reconstruction code written on-site and commercial fitting software (LCModel; Provencher, 1993). In addition to GABA, *N*-acetylaspartate (NAA), choline (Cho), and a combined measure of glutamate (Glu) and glutamine (Gln) referred to as Glx, also were examined. To quantify GABA, the difference-edited spectra were fitted with LCModel using basis sets acquired at 4T. The individual "ON" and "OFF" averages were frequency- and phase-corrected by using the NAA resonance of the interleaved "OFF" spectra as a navigator. The phase- and frequency-correction factors from the "OFF" NAA resonance for each averaged group were used for both the "ON" and "OFF" datasets. This was necessary since the NAA resonance was saturated in the "ON" spectra due to the frequency-selective Gaussian editing pulse applied at 1.89 ppm. This strategy has proven effective in tracking and correcting for motion artifacts throughout the 13-min acquisition which otherwise would result in imperfect subtraction and contamination of the difference-edited GABA signal with creatine (Cr) at 3.00 ppm. All corrected "ON" and "OFF" spectra then were averaged separately to produce a single 68 ms "ON" and "OFF" spectrum, which subsequently was subtracted to produce the final, optimized, difference-edited GABA spectrum. The appropriate LCModel templates were used to fit the 68 ms "OFF" spectrum and the difference-edited GABA spectrum. The GABA resonance at 3.00 ppm was normalized to the fitted Cr resonance from the 68 ms sub-spectrum. The total Cho peak (a combination of choline and phosphocholine) at 3.2 ppm, as well as the co-edited glutamate (Glu) and glutamine (Gln) peaks at 3.75 ppm and ~2.3 ppm, respectively, also were normalized to the fitted Cr resonance from the 68 ms "OFF" sub-spectrum. Glx was computed as Glu + Gln. The stability of Cr was assessed relative to NAA or as a "total" (i.e., the sum of NAA, Cho, Cr, NAA and Glu) using the unedited TE = 69 ms spectrum. Fig. 1A shows representative spectra from both voxels of interest.

2.3.3. Image segmentation

The high-resolution T_1-weighted images were segmented into grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF) compartments using the segmentation tool in the commercial software package FSL 4.1 (FMRIB Software Library; Analysis Group, FMRIB; Oxford, UK). The volumetric tissue contribution for each oblique voxel was determined and relative contributions of GM and WM were calculated using in-house software.

2.4. Assessments

Participants answered a series of questionnaires in order to provide information about the drug-induced effects on mood and interoceptive states they were experiencing. Directly after each scanning session participants answered the Profile of Mood States (POMS) to assess tension-anxiety, depression-dejection, anger-hostility, fatigue, vigor, and confusion-bewilderment (McNair et al., 1971). Hourly questionnaire sets included a shortened version of the Addiction Research Center Inventory (ARCI) as well as an investigator-constructed visual analog scale (VAS). The ARCI is a standardized set of scales intended to evaluate the stimulant-like (Benzedrine group: BG), amphetamine-like (AMPH), euphoric (Morphine-Benzedrine group: MBG), sedative- or intoxicating-like (Pentobarbital-Chlorpromazine-Alcohol group: PCAG), and psychotomimetic or dysphoric (Lysergic acid diethylamide: LSD) effects of drugs (Jasinski, 1977). The VAS required participants to rate how the drug made them feel with respect to 15 adjectives by placing a mark on a 100-mm continuum anchored by "not at all" or "extremely" at either end. Questionnaires were administered on Macintosh computers running in-house software (Study Log Master v.79).

2.5. Statistical analyses

The primary metabolite of interest was GABA, while NAA, Cho, and Glx were of secondary interest. Measurements were made two times during one study visit in order to assess the effect of zolpidem on metabolites under each condition (SSRI + placebo, i.e., baseline vs. SSRI + zolpidem). Data were analyzed by separate *t*-tests unless data violated assumptions of normality; then the Signed Rank test was used.

POMS data were collected once during each treatment condition while ARCI and VAS data were collected repeatedly over the course of the experimental session. Data were collapsed such that the time points directly before and after each scan were considered "placebo" and "zolpidem", respectively. These data were analyzed using paired *t*-tests.

Associations between measures of interest were examined. Change scores were calculated for GABA and behavior, and their relationships were investigated using Spearman's rho (ρ) due to the ordinal nature of the scales.

Standard statistical software (SigmaStat 3.1; Systat Software, Inc.; San Jose, CA) was used and alpha was set at 0.05.

3. Results

3.1. Participant characteristics

Depressed participants who completed this study could be considered partial responders on their maintenance therapy. They scored an average ± SD of 13.3 ± 13.9 (mild mood disturbance) on the Beck Depression Inventory (BDI) and 13.6 ± 11.5 (mild depression) on the