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Research paper

Cognitive effects of mifepristone in overweight, euthymic adults with depressive disorders

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ABSTRACT

Background: Previous studies have shown that individuals with mood disorders have a higher prevalence of both hypercortisolemia and insulin resistance. Insulin resistance is posited to contribute to the cognitive deficits observed in individuals who have depression. However, the mechanistic relationship between cortisol and insulin within the central nervous system remains to be further elucidated. This study aimed to evaluate the effects of the antiglucocorticoid agent, mifepristone, on metabolic function and cognitive performance in individuals receiving treatment for depressive disorders who were euthymic at baseline.

Methods: Participants were administered a 600 mg/day dose of mifepristone for 28 days. Oral glucose tolerance tests (OGTTs) and cognitive assessments measuring verbal memory and executive functioning were administered at baseline and after 28 days of treatment.

Results: Improvements in attention and verbal learning were associated with reduction of fasting plasma glucose (FPG) in response to mifepristone treatment.

Limitations: Limitations include the open-label design of this study and a small sample size.

Conclusions: The findings from this study suggest that improvement in fasting plasma glucose levels, upon administration of mifepristone, is associated with the improvement in early input of verbal information. Further studies are warranted in order to better evaluate the use of mifepristone or other antiglucocorticoid agents in treatment of mood disorders characterized by metabolic dysfunction.

1. Introduction

Individuals with mood disorders are known to exhibit high cortisol levels (Young, 2004; Young et al., 2004; Sapolsky, 2000). Cortisol, a glucocorticoid released by the adrenal cortex in response to stress, is a negative regulator of the hypothalamic-pituitary-adrenal (HPA) axis (Young, 2004; Tatomir et al., 2014). Dysregulation of the HPA axis results in elevated cortisol levels, which are thought to contribute to the depressive symptoms and cognitive impairment associated with mood disorders (Young, 2004; Tatomir et al., 2014; Wolkowitz et al., 1990; Sapolsky, 2000). Therefore, medications that lower cortisol levels are under investigation as potential treatment options for these individuals.

There is accumulating evidence suggesting that the synthetic steroid compound mifepristone may have anti-depressant and cognition-enhancing effects in individuals with mood disorders (Young et al., 2004; Block et al., 2017; Flores et al., 2006; Belanoff et al., 2002,2001). Mifepristone is a peripheral progesterone receptor antagonist (Belanoff et al., 2002; Young et al., 2004). However, at higher doses, mifepristone acts as a glucocorticoid receptor antagonist, attenuating cortisol action by preventing cortisol from binding to the glucocorticoid receptor (Belanoff et al., 2002; Young et al., 2004). Previous studies have found that mifepristone may improve depressive symptoms and enhance neurocognitive functioning in people with bipolar disorder, as well as in people with Cushing's syndrome, another disorder characterized by primary hypercortisolemia (Young et al., 2004; Block et al., 2017; Belanoff et al., 2002, 2001).

In addition to elevated cortisol levels, persons with mood disorders have a higher prevalence of insulin resistance (IR), a condition in which central and peripheral nervous system tissues become increasingly unresponsive to the effects of insulin (Rasgon et al., 2016). In particular, the link between IR and depression has been studied by us and others (Block et al., 2017; Flores et al., 2006; Wroolie et al., 2015; Lin et al., 2015; Rasgon and Kenna, 2005; Webb et al., 2017). Because IR affects areas of the brain involved in memory and attention, IR is thought to play a role in the cognitive deficits experienced by individuals with depression (Lee et al., 2016; Wroolie et al., 2015; Craft,

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2006). Even in individuals with remitted depression, these cognitive deficits in verbal memory and attention remain (Lam et al., 2014; Wroolie et al., 2015; Gold et al., 2005).

Given that elevated cortisol levels increase the risk of IR (Geer et al., 2014; Zhou et al., 2016), and that both high cortisol levels and IR have been implicated in depressive disorders (Young, 2004; Rasgon and McEwen, 2016; Belanoff et al., 2001; Block et al., 2017; Wroolie et al., 2015), reduction of cortisol levels might be one way to improve not only insulin sensitivity, but also depressive symptoms and cognitive functioning in individuals with depressive disorders. Here we conducted a 28-day open-label study using mifepristone to evaluate the effect of cortisol reduction on memory and attention in people with a history of depressive disorders and who were euthymic at baseline. To further investigate the mechanistic relationship between cortisol and insulin, we sought to compare changes in cognitive functioning after mifepristone treatment between individuals who were insulin resistant and those individuals who were insulin sensitive.

2. Methods

The Stanford University Institutional Review Board approved the current study in its entirety. All participants provided informed consent prior to study enrollment after they received detailed information regarding all study procedures, potential side effects of study medication, risks and benefits of participation, and contact personnel in case of questions or concerns. Study participants were recruited through the clinics within the Department of Psychiatry and Behavioral Sciences at Stanford University.

Inclusion criteria included men and women between the ages of 45 and 70 years old with a BMI greater than 25 kg/m^2. All participants had recently experienced a major depressive episode (MDE) for which they were receiving treatment as prescribed by their personal physicians but did not meet DSM-V criteria for MDE within the past 4 weeks.

Exclusion criteria included diagnosis of possible or probable cognitive impairment, women who were pregnant or breastfeeding, history of Type I or Type II Diabetes, unstable cardiovascular disease or history of myocardial infarction within the past year, significant cerebrovascular disease as evidenced by neurological examination, uncontrolled hypertension, current drug or alcohol abuse, history of neurological disorders (e.g. multiple sclerosis, stroke, etc.), use of any drug that may significantly affect psychometric testing or insulin testing, current use of Wellbutrin or Adderall, and history of a manic episode during the past year.

2.1. Procedures

Participants were administered a 600 mg/day dose of open-label mifepristone for 28 days. Metabolic and cognitive data were collected at baseline (time 1) and after 28 days of medication treatment (time 2).

2.1.1. Glucose metabolic assessment

To assess metabolic function, participants received an Oral Glucose Tolerance Test (OGTT) at baseline and after 28 days of medication treatment. The OGTT is designed to measure how effectively cells respond to and remove glucose from the blood. Participants' blood glucose levels were measured prior to and 120 minutes after ingesting a 75-gram glucose solution. Fasting Plasma Glucose (FPG) and Fasting Plasma Insulin (FPI) are the glucose and insulin values, respectively, measured after participants have fasted for at least 8 hours prior to the start of the OGTT and OGTT-120 is the glucose value measured 120 minutes after ingesting the glucose solution, which can signify impaired glucose tolerance. FPG, FPI, and OGTT-120 results are shown in Table 2.

2.1.2. Neuropsychological assessment

Participants also underwent cognitive testing at baseline and after 28 days of medication treatment. Validated measures of verbal memory and executive functioning, specifically cognitive flexibility were administered and included the following: California Verbal Learning Test (CVLT): 1st trial learning, trials 1-5, short delay free recall, and long delay free recall and Delis-Kaplan Executive Function System (D-KEFS): Trail Making Test: Condition 4 (Number-Letter Switching). Depressive status was evaluated at baseline using the 21-item Hamilton Depression Rating Scale (Ham D-21) (Hamilton, 1980).

2.2. Statistical analyses

Clinical, demographic, and neuropsychological data analyses were performed using SPSS software version 24.0 (SPSS Inc., Chicago, IL). Pearson correlations were utilized to assess FPG, OGTT, and FPI at time 1 with age, education, BMI, and cognitive variables. Cognitive variables were analyzed for normality using 1-sample Kolmogorov-Smirnov test and log transferred if found not to be normally distributed. Regression analyses were then conducted using age, education, BMI, individual time 1 cognitive variables and change in FPG or OGTT as predictors to determine whether there were treatment effects on any time 2 cognitive variables in relation to FPG or OGTT change. Similar regression analyses with FPI were not possible due to insufficient data points at time 2.

3. Results

Sixty participants were screened, 23 participants were enrolled, and 13 participants (3 men, 10 women) completed the study (see Fig. 3). Ten participants withdrew from the study. Only one subject withdrew for an adverse event. There were no differences between those participants who completed the study and those who withdrew.

Age, sex, education, BMI, and depressive symptom severity at time 1 are shown in Table 1, and the metabolic measures are shown in Table 2.

No significant correlations were found between FPG or FPI at time 1 and age, education, BMI, time 1 Ham D-21, FPG at time 2, or any cognitive variables. Similarly, no significant correlations were found between OGTT-120 at time 1 and age, education, BMI, time 1 Ham D-21, OGTT-120 at time 2, or any cognitive variables. A significant correlation was found between time 1 FPI and BMI ($r = 0.76$, $p = .01$). No significant differences were found between time 1 and time 2 FPG ($t = -1.03$, $p = .22$) or between time 1 and time 2 OGTT-120 ($t = 0.94$, $p = .37$) using paired sample t-tests.

Regression analyses using age, education, BMI, and change in FPG as predictors, revealed that a decrease in FPG from time 1 to time 2 significantly predicted improvement in verbal attention (CVLT 1st trial learning; see Table 3 and Fig. 1). Similarly, a decrease in FPG from time 1 to time 2 predicted improvement in verbal learning (CVLT trials 1–5; see Table 4 and Fig. 2). There were no other significant or trend level findings for other cognitive variables in relation to FPG. No significant or trend level findings were shown for change in OGTT-120 using similar regression analyses.

4. Discussion

This study was based on prior evidence that mifepristone may have anti-depressant and cognition-enhancing effects in individuals with

Table 1
Demographics of the 13 subjects who completed the study.

	Range	Mean	SD
Age	45–70	59.92	7.96
Years of Education	12–18	16.15	1.91
BMI	21.80–52.30	33.35	9.23
Time 1 Ham-D	1–20	9.82	5.6