Tryptophan Depletion and Risk of Depression Relapse: A Prospective Study of Tryptophan Depletion as a Potential Predictor of Depressive Episodes

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Background: This study investigated the relationship between depressive symptom response during tryptophan depletion and future depressive episodes.

Methods: Twelve subjects with prior major depressive episodes in remission and medication-free for ≥3 months (patients), and 12 matched healthy (control) subjects received two tryptophan depletion tests 1 week apart. During follow-up the Hamilton Depression Rating Scale was administered weekly for 1 month, monthly for 3 months, and once at 6 and 12 months.

Results: With results from both tests, tryptophan depletion has a sensitivity of 78%, specificity of 80%, positive predictive value of 70%, and negative predictive value of 86% to identify future depressive episodes. Survival analysis shows that mood response to tryptophan depletion reliably predicts major depressive episodes during the follow-up year ($r = .2725, p = .014$).

Conclusions: Tryptophan depletion may be clinically useful in identifying individuals at risk for future major depressive episodes. Biol Psychiatry 2000;48:327–329 © 2000 Society of Biological Psychiatry

Key Words: Vulnerability, major depression, serotonin, depletion paradigm

Introduction

The development of procedures to identify individuals at biological risk for depression is highly desired. A variety of distinctive clinical features and laboratory findings have been proposed as potential predictors of major depressive episodes (MDEs; Horwath et al 1992; Keller et al 1983; Rush et al 1997). Although such tests have contributed to a better understanding of the pathophysiology of depression, their clinical application is limited. Brain serotonin levels are dependent on plasma levels of tryptophan (TRP; Curzon 1981). Tryptophan depletion has been shown to induce mild depressive symptoms in 30% of subjects with a family history of mood disorder, but does not affect healthy subjects without personal or family history of mood disorder (Benkelfat et al 1994). Tryptophan depletion also has been shown to induce depressive symptoms in medication-free subjects in remission from at least one prior MDE (Moreno et al 1999; Smith et al 1997). If subjects “at risk” for MDEs experience temporary depressive symptoms during TRP depletion and healthy control subjects do not (Benkelfat et al 1994; Moreno et al 1999), TRP depletion may help to identify vulnerable individuals.

Methods and Materials

Subjects

Twelve subjects with a past history of at least one MDE but in clinical remission and medication free for at least 3 months and 12 age- and gender-matched control subjects with no personal or family history of any mental disorder participated in this study. After complete description of the study to the subjects, and discussion of the possibility of experiencing depressive symptoms lasting from 6 to 24 hours during testing, written informed consent was obtained. The screening methods, and demographic and clinical characteristics of the subjects have been described in a previous report detailing the acute mood response to TRP depletion (Moreno et al 1999).

Procedure

DEPLETION. Subjects underwent two TRP depletion tests, separated by 1 week. One test used a 102-g, TRP-free, 15–amino acid drink to accomplish full TRP depletion (full-strength test). The other test involved a control preparation—a proportionally identical 25-g, TRP-free, 15–amino acid drink (quarter-strength test). This alternative control preparation was used due to a U.S. Food and Drug Administration ban on the use of TRP at the time.
the study was conducted. The experiment was conducted in a double-blind, crossover fashion, using a randomly assigned sequence of full- and quarter-strength tests. Behavioral ratings were obtained at baseline and at 5, 7, and 28 hours after the depletion drinks (Moreno et al. 1999).

**FOLLOW-UP.** Subjects were monitored for depressive symptoms using the 25-item Hamilton Depression Scale (HAM-D; Mazure et al. 1986) weekly for 1 month, and then monthly for 3 months. Retrospective HAM-D and Structured Clinical Interview for DSM-III-R (Spitzer 1987); depressive disorder section) interviews were performed at 6 and 12 months. Recurrence was defined as a return of symptoms of enough duration and severity to meet DSM-III-R criteria for an MDE, plus a doubling in HAM-D score with a total score $\geq 18$.

**Data Analysis**

**MOOD RESPONSE DURING TRP DEPLETION.** As in prior studies, the highest HAM-D score observed during testing minus the baseline score was used for analysis. Post hoc iterations suggested that a change in HAM-D score of more than 5 points could be a reliable categoric marker for the prediction of a future depressive episode. Data were analyzed for each drink dose (quarter and full strength) and for both doses combined (selecting the highest “peak score”). To determine whether this categoric criterion would accurately separate individuals with a vulnerability for a future MDE from those without, a receiver operating characteristic analysis (Metz 1986) was performed comparing various change criteria to the peak score. Fisher’s exact test was used to test the differences in frequency of new MDEs between categorical responders to TRP depletion and nonresponders. Survival analysis was performed using the Cox regression method.

**Results**

The acute biochemical and depressive effects of TRP depletion were transient, and subjects returned to baseline mood within 12 to 24 hours. No serious adverse events were observed, and no subject required treatment in response to TRP depletion. These data have been presented in a separate publication (Moreno et al. 1999). A graphic presentation of HAM-D scores is included in Figure 1.

Nine of 24 subjects developed a new depressive episode in the year following TRP depletion. This included seven of 10 depletion responders (six patients and one control subject) and two of 14 depletion nonresponders (one patient and one control subject). Fisher’s exact test comparing both groups shows this difference to be statistically significant ($p = .01$). An increase in HAM-D of more than 5 points during depletion most accurately predicted depressive episodes in the follow-up year. Receiver operating characteristic analysis (Metz 1986) indicated that this cutoff was appropriate, with an area under the curve of .59 ± SD of .13 for the quarter-strength test, .70 ± .11 for the full-strength test, and .77 ± .10 for the highest peak score from either test. Full-strength TRP depletion has a sensitivity of 60%, a specificity of 80%, a positive predictive value (PPV) of 66%, and a negative predictive value (NPV) of 75% for prediction of depressive episodes in the following year. On the other hand, quarter-strength TRP depletion has a sensitivity of 44%, specificity of 80%, PPV of 57%, and NPV of 71%. With selection of the highest response from either test, TRP depletion has a sensitivity of 78%, a specificity of 80%, a
Risk for future depression. Although the inherent risk of temporary induction of depressive symptomatology demands a very careful approach to these studies, the payoff of developing a tool that may potentially detect individuals who are vulnerable to developing depressive episodes may easily justify this approach. This may in turn allow for preventive strategies to be employed that diminish the suffering and disability associated with depression in a way similar to an exercise treadmill test or a glucose tolerance test that aids the diagnosis and treatment of coronary artery disease and diabetes, respectively.

References


