Effect of Tryptophan Depletion on Smokers and Nonsmokers With and Without History of Major Depression

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Background: *Serotonergic dysregulation is posited to contribute to comorbidity between nicotine dependence and depression. We tested whether acute tryptophan depletion (ATD) triggers depressive symptoms in euthymic, unmedicated smokers and nonsmokers with and without history of major depressive disorder (MDD).*

Methods: *Acute tryptophan depletion and taste-matched placebo challenges were administered double-blind in counter-balanced order. Participants were four groups of volunteers hypothesized to be of increasing affective vulnerability as follows: nonsmokers lacking recurrent personal and familial history of MDD (n = 20), smokers lacking recurrent personal and familial history of MDD (n = 21), nonsmokers with history of recurrent personal and familial MDD (n = 16), and smokers with recurrent personal and familial history of MDD (n = 16). Depression, dysphoric mood, and plasma amino acids were measured at baseline and around the time of peak depletion.*

Results: *Depressive symptom response to ATD was heightened significantly by history of MDD ($p < .001$) and marginally by smoking ($p = .09$). Smoking seemed to magnify the ATD response of those with a history of MDD (effect size = .63) but had no effect on those without MDD history (effect size = .06).*

Conclusions: *Depressive symptom response to serotonergic challenge is exaggerated in unmedicated, euthymic adults with recurrent personal and familial vulnerability to MDD, perhaps especially if they also smoke.*

Key Words: Serotonin, nicotine dependence, cigarette smoking, tryptophan depletion, vulnerability, major depression

Major depressive disorder (MDD) is strongly associated with cigarette smoking and nicotine dependence in community and treatment samples (Breslau et al 2004; Hitsman et al 2003). Shared genetic factors influence the development of co-occurring smoking and MDD (Kendler et al 1993). Additionally, there might be a bidirectional, experiential causal relationship between the two conditions, because MDD heightens the risk of starting smoking and smoking increases the risk of developing MDD (Kendler et al 1993). A shared abnormality of serotonin (5-HT) neurotransmission could mediate the coexistence of the two disorders (Markou et al 1998). A functional deficiency in 5-HT has been implicated in the pathophysiology of major depression (Delgado et al 1994). Findings from animal, pre-clinical, and treatment studies of nicotine dependence suggest that 5-HT also plays a role in regulating smoking behavior, craving, and nicotine withdrawal (Harrison et al 2001; Hitsman et al 2005; Killen et al 2001).

Acute tryptophan depletion (ATD), which transiently reduces brain 5-HT synthesis, has been studied as a provocational challenge to elicit signs of underlying affective vulnerability. In most studies (Lam et al 1996; Moreno et al 1999; Neumeister et al 2004; Smith et al 1997), although not all (Leyton et al 1997), ATD has been shown to trigger a clinically significant increase in depressive symptoms 5 to 7 hours after challenge among euthymic adults who have a personal history of mood disorder. Similarly, individuals who are asymptomatic but have a family history of depression exhibit a depressive response to ATD (Benkelfat et al 1994; Klaassen et al 1999). A stronger magnitude depressive response to ATD is predicted by a history of recurrent as opposed to single depressive episodes, prior or current treatment with selective serotonin re-uptake inhibitors, previous suicidal thoughts/attempts, and being female (Booij et al 2002). The presence of neuroticism, a personality trait strongly associated with both smoking (Goodwin and Hamilton 2002) and current depression (Huezo-Diaz et al 2005), also intensifies the mood response to ATD among individuals with a family history of depression (Stewart et al 2002), as does the presence of the short allele on the promoter region of the 5-HT transporter gene (5-HTTLPR-S) (Neumeister et al 2002).

Some evidence suggests that cigarette smoking might be associated with a similar serotonergically mediated, affective vulnerability to depressive symptoms. Smokers with a history of MDD report more severe nicotine withdrawal symptoms during prior quit attempts compared with smokers who lack a depressive vulnerability (Madden et al 1997). Treatment with serotonergic agents can improve mood in smokers (Dalack et al 1995) and prevents or minimizes the increased dysphoric mood that is ordinarily precipitated by withdrawing nicotine (Bowen et al 1991; Killen et al 2001; Spring et al 1991). Smoking cessation treatment via the selective serotonin re-uptake inhibitor fluoxetine selectively benefits smokers who exhibit greater depressive symptoms pretreatment (Hitsman et al 1999). Also, a higher level of neuroticism and the presence of the 5-HTTLPR-S genotype are associated with difficulty quitting smoking (Hu et al 2000).

The present study tested the hypothesis that, among euthymic adults, a personal and familial history of MDD and current cigarette smoking would both be associated with an affective vulnerability to respond to a serotonergic challenge by exhibiting

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depressive symptoms. The diatheses for major depression and smoking were expected to exert additive effects on the affective response to ATD. Specifically, the magnitude of depressive response to ATD was expected to increase as a function of increasing affective vulnerability as follows: 1) nonsmokers lacking a recurrent personal and familial history of MDD, 2) smokers lacking a recurrent personal and familial history of MDD, 3) nonsmokers with a history of recurrent personal and familial MDD, 4) smokers with a history of recurrent personal and familial MDD.

Methods and Materials

Eligibility Screening

Community volunteers telephoned the study in response to flyers and newspaper advertisements seeking adult smokers and nonsmokers between the ages of 18 and 65. They were informed that participation required three screening visits and two 8-hour experimental sessions "to determine whether smokers and nonsmokers experience changes in mood and food intake after drinking an amino acid beverage." Payment for completing the study was $100. Mailed screening questionnaires included a medical history form, Beck Depression Inventory (BDI) (Beck et al 1961), and Fagerstrom Tolerance Questionnaire to assess nicotine dependence (Fagerstrom 1978).

Study candidates attended a first in-person screening appointment at which time they gave written informed consent to participate after receiving a full description of the study. The Hines Hospital Institutional Review Board approved the study protocol. Participants were trained to record cigarette intake and had blood drawn for medical screening. They attended a second screening visit at which medical eligibility was evaluated by a physician and a third visit at which personal and familial psychopathology were assessed. Candidates' current depression was evaluated by the 21-item Hamilton Depression Scale (HAMD) (Hamilton 1967). Lifetime personal history of psychopathology was assessed via the Structured Clinical Interview for DSM-IV (SCID) (Williams et al 1992) mood, anxiety, and substance-related disorders modules. First-degree relatives' history of psychopathology was evaluated by the semi-structured Family History Interview (FHI) (Endicott et al 1975).

Following the procedure of Litt et al (1990), interviewers also elicited autobiographical information that was subsequently scripted to induce negative moods during the two experimental sessions. Participants described several events within the past year that made them "anxious, angry, or sad." With 10-point scales, they rated the intensity of upset that each event caused and the vividness of the image generated. Two events that rated $>$ five and of comparable intensity and vividness were selected and scripted into guided images.

Four groups of euthymic participants were identified: 20 nonsmokers without a personal or familial history of recurrent DSM-IV MDD, 21 smokers without recurrent personal or familial history of MDD, 16 nonsmokers with recurrent personal and familial history of MDD, and 16 smokers with recurrent personal and familial history of MDD. Smokers were required to have smoked more than 10 cigarettes per day for the past year. Nonsmokers could never have smoked on a regular basis. To be classified as positive for depression history, participants needed to have had both a personal and familial history of MDD. Personal history was defined as $\geq$ two episodes (one within the last 5 years but not within the last 2 months, and the other within the past 10 years). Family history of depression was defined as having one or more first-degree relative with known MDD. Participants negative for history of depression were required to have no lifetime personal or familial history of MDD.

Exclusion criteria were: pregnancy or lactation, history of severe food allergies, current use of nicotine replacement, alcohol or drug treatment within the last year, overweight $>$ 60 pounds, history of neurological condition, clinically significant medical condition, current psychiatric disorder (other than nicotine dependence) or psychotropic medication use, past psychiatric disorder other than MDD, HAMD $>$ 14, or BDI $>$ 15. The study sample represented 31% of those screened (73 of 235). There was no attrition, perhaps in part because compensation for participation was contingent upon completion of both test sessions.

Experimental Sessions

The ATD and placebo challenge drinks were administered double-blind and in counterbalanced order on different test days separated by 1 week. Female participants completed the study between days 7 and 21 of their menstrual cycle. Table 1 shows the time line for ATD and placebo test sessions. After a 12-hour overnight fast, participants came to the laboratory at 8:00 AM, underwent baseline assessment of depression and mood, and had blood drawn to assess plasma amino acids.

At 9:30 AM, they ingested one of two challenges. The ATD mixture consisted of 15 amino acids: l-alanine (5.5 g), l-arginine (4.9 g), l-cystine (2.7 g), glycine (3.2 g) l-histidine (3.2 g), l-isoleucine (8.0 g), l-leucine (13.5 g), l-lysine monohydrochloride (11.0 g), l-methionine (3.0 g), l-phenylalanine (5.7 g), l-proline (12.2 g), l-serine (6.9 g), l-threonine (6.9 g), l-tyrosine (6.9 g), and l-valine (8.9 g). Three amino acids—methionine, cystine, and arginine—were encapsulated (because their unpalatable taste could not be masked) and ingested 15 min before the challenge beverage. The remaining amino acids were mixed with 1/3 cup tonic water, 4 drops peppermint extract, 1 Tbsp. Hershey's chocolate syrup, and 5 small ice cubes. In the placebo condition, participants ingested identical capsules containing confectioner's sugar, followed 15 min later by the placebo mixture consisting of 5/6 cup tonic water, 5 drops peppermint extract, 1 tbsp Hershey's chocolate syrup, 2 tsp baking soda, 1 tbsp psyllium (unflavored Metamucil), and 7 small ice cubes.

Table 1. Timeline of ATD or Placebo Challenge Session

Time	Hours After Challenge	Procedure
8:00 AM	−1.5	Baseline testing (depression, mood, plasma amino acids)
9:30 AM	0	Consumption of amino acid or placebo mixture
12:30 PM	3	Assessment of mood
1:30 PM	4	Reading materials removed from observation room
2:30 PM	5	Negative mood induction followed by repetition of depression and mood assessments and blood sampling for amino acids
4:30 PM	7	Depression and mood assessments
5:30 PM	8	Assessment of mood
6:00 PM	8.5	Nutritionally balanced repletion meal
6:30 PM	9	Assessment of post-repletion depression, participant released

ATD, acute tryptophan depletion.