Acute tryptophan depletion in depressed patients treated with a selective serotin-noradrenalin reuptake inhibitor: Augmentation of antidepressant response?

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Brief report

Acute tryptophan depletion in depressed patients treated with a selective serotonin–noradrenalin reuptake inhibitor: Augmentation of antidepressant response?

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Abstract

Background: It has frequently been demonstrated that experimental lowering of serotonin (5-HT) neurotransmission by acute tryptophan depletion (ATD) induces a transient depressed mood in 50–60% of patients treated with a selective serotonin reuptake inhibitor (SSRI) who are in remission from depression. In unmedicated depressed patients, ATD has no immediate effect on symptoms. The effects in currently depressed medicated patients have not been investigated.
Methods: Fourteen currently depressed patients (seven patients treated with a selective serotonin–noradrenalin reuptake inhibitor (SSNRI); seven other treatment, non-SSNRI) received ATD in a double-blind, crossover design. Different strengths of the ATD mixture (aimed at 50% and 90% reduction of tryptophan) were used on separate days. Psychiatric symptoms were assessed at both sessions prior to, at +6.5 h, and at +24 h after ATD.
Results: The ATD mixtures induced the expected reductions of plasma tryptophan levels. Full but not partial depletion improved mood and other psychiatric symptoms at +24 h in patients who received SSNRI treatment, as indicated by clinical ratings and self-report. Subjective sleep quality also improved.
Conclusions: The effects of ATD on psychiatric symptoms in currently depressed patients are remarkably different from the results in recently remitted SSRI-treated patients. ATD in currently depressed patients treated with serotonergic antidepressants possibly provides important information about the mechanism of action of SSRIs.

Keywords: Serotonin; Tryptophan; Depression; Augmentation; Pindolol; Venlafaxine; SSRI

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1. Introduction

Acute tryptophan depletion (ATD) induces a transient depressed mood in some patients who are in remission from depression (Van der Does, 2001; Booij et al., 2002, 2003). In recently remitted patients, the probability of ATD response is highest in patients treated with a selective serotonin reuptake inhibitor (SSRI) (Delgado et al., 1990, 1999). Three studies investigated ATD in currently depressed patients, and all reported no mood effects on the depletion day (Delgado et al., 1994; Price et al., 1997, 1998). However, Delgado et al. (1994) reported a worsening of mood on the next day in one third of the patients, whereas one fourth showed a clinical improvement, and the direction of change was predictive of treatment responsiveness. This bimodal delayed mood effect was not found in the two other studies (Price et al., 1997, 1998); however these included a 5-HT challenge at the point of maximal depletion. This indicates that ATD in currently depressed patients may cause a compensatory upregulation of 5-HT receptors.

Considering its potential clinical relevance, a replication of the study by Delgado et al. (1994) is warranted. However, because it is very difficult to recruit medication-free depressed patients in secondary settings, we explored the effects of ATD in currently depressed patients treated with medications acting on the 5-HT system. There is a reason to believe that the effects of ATD in medicated symptomatic patients may be different from the effects in unmedicated patients and patients in remission. The 5-HT1A antagonist pindolol has been found to accelerate the therapeutic effects of antidepressants that affect the 5-HT system, especially in the first 2 weeks of treatment (Artigas et al., 2001; Ballesteros and Callado, 2004). Depletion of 5-HT decreases 5-HT synthesis (Nishizawa et al., 1997) and may increase postsynaptic activity in unmedicated patients, as shown by the response to a 5-HT challenge after ATD (Price et al., 1997, 1998). ATD in currently SSRI-treated patients may accelerate the desensitization process, and consequently accelerate therapeutic response.

In conclusion, we hypothesized that ATD would improve symptoms in currently depressed patients treated with serotonergic antidepressants, and would have no effect in depressed patients who receive other treatments.

2. Materials and methods

2.1. Participants

Eligible patients were outpatients of a mood disorders clinic. Inclusion criteria were: age between 18 and 65 years, met DSM-IV criteria for current depression, Hamilton Depression Rating Scale (HRSD, 17 items) (Hamilton, 1960) >15, or Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) >17. Exclusion criteria were: substance abuse within the past 3 months, psychosis (lifetime), physical illness, lactation, and pregnancy. Clinical background variables and diagnoses were assessed with the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1995).

2.2. Amino acids

At each depletion session, patients received in randomized order either 100 g or 25 g of ATD mixture (cf. Booij et al., 2005). The composition of the 100 g mixture was similar as in Delgado et al. (1990). The 25 g mixture consisted of the same amino acids (AAs) but in one quarter amount (Krahn et al., 1996).

2.3. Instruments

Symptoms were assessed using the Comprehensive Psychopathological Rating Scale (CPRS) (Goekoop et al., 1992). The CPRS is a 68-item interview/observation scale with items ranging from 0 to 6, including the MADRS (Montgomery and Asberg, 1979) and the Brief Anxiety Scale (BAS) (Tyrer et al., 1984). Factor-analytic research has revealed that the CPRS consists of six factors (Goekoop et al., 1992). The 17-item HRSD (Hamilton, 1960) was also administered. Self-report measures included the Beck Depression Inventory II (BDI-II) (Beck et al., 1996), the Positive and Negative Affectivity Scale (PANAS) (Watson et al., 1988), and

Table 1
Scheme of the ATD procedure

Time	Assessment
±1 week before ATD	Informed consent, intake session including symptom questionnaires and SCID
−24 h	Low Trp diet (160 mg/day) until next day
−1 h	Symptom assessments, blood sample
0 h	ATD mixture (25 g or 100 g)
+6 h	Blood sample
+6.5 h	Symptom assessments
+7.5 h	End of session and dietary restrictions
+24 h	Symptom assessments, blood sample

This procedure was repeated about 1 week later; those who had received the 100% mixture received the 25% mixture and vice versa. SCID=Structured Clinical Interview for DSM-IV; ATD=acute tryptophan depletion.

a list of 48 physical symptoms on a five-point scale ranging from 0 (absent) to 4 (very intense). All questions referred to the symptoms at the moment of assessment. Clinical ratings were performed by a rater who was blind to the sequence of the mixtures and to the study hypothesis.

Venous blood was obtained to determine total plasma tryptophan (Trp) and the ratio of Trp/large neutral amino acids (LNAA).

2.4. Procedure

The procedure was identical as in Booij et al. (in press), and is summarized in Table 1.

2.5. Statistical analyses

The outcome variables were analyzed by general linear models (GLM) for repeated measures, using intervention (100 g AA vs. 25 g AA) and time of assessment (pre vs. post depletion vs. the next day) as within-subjects factors. Non-parametric tests were used when necessary.

3. Results

3.1. Patients

Sixteen patients were included. Two SSRI-treated patients (both full depletion session) dropped out after the first session. One patient found the ATD session too tiring; another patient was unable to schedule the second session within a reasonable time interval. The clinical characteristics of the remaining patients (seven SSNRI, seven other treatments–no SSRIs) are summarized in Table 2. There were no baseline group differences.

Table 2
Clinical and demographic characteristics of the sample (n=14)

	SSNRI	Non-SSNRI
M/F	2/5	3/4
Age (S.D.)	46.1 (8.7)	43.1 (10.0)
Type of medication	Venlafaxine (n=5)	None (n=4)
	Venlafaxine+ lithium (n=1)	Lithium (n=1)
	Mirtazapine (n=1)	TCA (n=2)
Duration of antidepressant treatment until full ATD session (S.D.)	37.6 (39.1) days[a]	Lithium: 3 years TCA: 7 days and 20 days
Diagnosis	6	4
Major depressive disorder	0	1
Bipolar disorder, type I, last episode depressive	1	2
Bipolar disorder, type II, last episode depressive		
Other diagnosis	2	2
Dysthymia	3	0
Anxiety disorder	2	0
Bulimia nervosa/binge eating disorder		
Single/recurrent episodes	2/5	3/4
Duration of current episode (months) ±S.D.	9.6 (5.7) [range 1–18]	22.6 (21.7) [range 1–60][b]
MADRS at intake (S.E.)	26.4 (2.9) [range 18–34]	23.4 (2.4) [range 18–41]
17-Item HRSD at intake (S.E.)	18.6 (1.1) [range 8–24]	17.1 (2.0) [range 15–22]
BDI-II at intake (S.E.)	34.9 (3.1) [range 13–45]	27.6 (4.3) [range 23–46]
Full depletion first	3	3

SSNRI=selective serotonin–noradrenalin reuptake inhibitor; TCA=tricyclic antidepressant; MADRS=Montgomery–Asberg Depression Rating Scale; HRSD=Hamilton Depression Rating Scale; BDI-II=Beck Depression Inventory—2nd edition.

[a] One patient used venlafaxine 75 mg/day for about 100 days before the full depletion session. Without this patient, the mean duration (S.D.) is 27.2 (10.2) days.

[b] Without the patient with the duration of episode of 60 months, the mean duration (S.D.) became 16.4 (15.5) days.

3.2. Biochemical measures

Full depletion reduced total Trp and the Trp/LNAA ratio by 85.9% (S.E.=2.8) and 93.3% (S.E.=2.6), respectively, at +6 h. During partial depletion, the average reductions were 57.8% (S.E.=3.2) and 57.1% (S.E.=3.9), respectively. At *t*(+24 h), Trp and Trp/LNAA levels were still reduced by 8.7% (S.E.=6.3) and 26.5% (S.E.=6.2) after full depletion, but were increased by 14.9% (S.E.=9.0) and 16.8% (S.E.=4.8) after partial depletion. No between-group differences were found.

3.3. Symptoms

SSNRI-treated patients reported a relief of symptoms at *t*(+24 h) after full depletion (Figs. 1 and 2; Table 3). The improvement occurred across a broad range of affective symptoms. Subjective sleep quality was notably improved. At *t*(+6.5 h), the CPRS subscale 'motivational disintegration' was slightly higher; this was due to an increase of the items 'elation,' 'labile emotional responses,' 'overactivity,' and/or 'elated mood' in four patients in this group. In the depressed patients treated otherwise, none of the symptom scales was affected at *t*(+6.5 h) or *t*(+24 h).

Nonparametric Wilcoxon tests between *t*(−1 h) and *t*(+24 h) for the full depletion condition in the SSNRI group revealed a similar pattern, but now the HRSD was also significant ($Z=-2.03$; $P=0.04$) and a trend was found for BDI total ($Z=-1.78$; $P=0.07$).

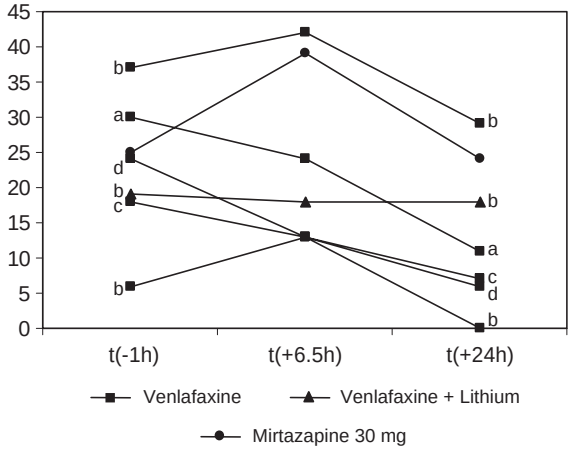

Fig. 1. MADRS scores during full depletion for SSNRI-treated patients. Score on the sleep item is not included. (a) 75 mg/day; (b) 150 mg/day; (c) 225 mg/day; (d) 275 mg/day.

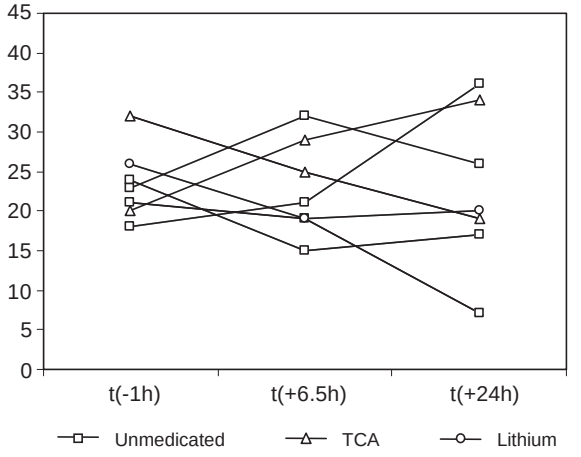

Fig. 2. MADRS scores during full depletion for non-SSNRI-treated patients. Score on the sleep item is not included.

4. Discussion

High-dose ATD improved symptoms in currently depressed patients treated with the SSNRI venlafaxine, whereas no effects were found in depressed patients receiving other treatments. The finding that depleting 5-HT relieves depressive symptoms may be counterintuitive, but is in line with the finding that 5-HT1A antagonists, like pindolol, accelerate the therapeutic response when given concomitantly with SSRIs in the early phase of antidepressant treatment (Blier, 2003). Acute SSRI administration initially activates somatodendritic 5-HT1A autoreceptors due to increased extracellular 5-HT, and, consequently, reduced 5-HT neuron firing activity. After prolonged administration, SSRIs desensitize presynaptic inhibitory 5-HT1 autoreceptors and downregulate postsynaptic 5-HT1A and 5-HT2 receptors, resulting in a normalization of 5-HT neuron firing activity (Blier and de Montigny, 1994). As ATD substantially reduces 5-HT levels in the brain (Nishizawa et al., 1997), ATD in medicated depressed patients–in whom autoreceptors may not yet have sufficiently been desensitized–may prevent the initial decrease in 5-HT neuron firing activity that usually occurs after

Table 3
Means (S.E.) of the mood questionnaires for the SSNRI-treated group, broken down by condition and time of assessment

Intervention	Partial ATD			Full ATD			Intervention by time
Questionnaire/time	*t*(−1 h)	*t*(+6.5 h)	*t*(+24 h)	*t*(−1 h)	*t*(+6.5 h)	*t*(+24 h)	*F*(*df*); *P*
CPRS							
Emotional dysregulation	30.3(3.8)	33.4(3.0)	31.9(5.5)	37.0(5.6)	35.4(6.8)	22.1(4.8)[a]	*F*(2,12)=5.2; *P*=0.02
Motivational inhibition	6.4(1.5)	7.3(0.9)	6.3(1.4)	7.1(1.3)	7.6(2.2)	5.4(1.8)	*F*(2,12)=0.4; *P*=0.65
Motivational disintegration	1.1(0.5)	0.4(0.2)	0.6(0.4)	0.0(0.0)	1.4(0.6)[b]	0.4(0.3)	*F*(2,12)=4.3; *P*=0.04
Perceptual disintegration	0.3(0.2)	0.4(0.3)	0.1(0.1)	0.4(0.3)	0.6(0.4)	0.0(0.0)	*F*(2,12)=0.2; *P*=0.73
Behavioral disintegration	2.0(1.0)	2.7(0.8)	1.7(1.1)	1.6(0.5)	1.9(1.2)	1.9(0.9)	*F*(2,12)=0.4; *P*=0.69
Autonomic dysregulation	4.1(0.8)	5.9(1.7)	6.9(1.9)	4.4(1.1)	6.1(2.1)	2.6(1.3)[a]	*F*(2,12)=3.1; *P*=0.08
MADRS	19.6(3.3)	22.9(2.0)	20.1(3.9)	22.7(3.7)	23.1(4.7)	13.6(4.0)[a]	*F*(2,12)=4.2; *P*=0.04
BAS	9.8(1.8)	11.1 (2.5)	13.6(3.0)	11.8(1.8)	11.6(3.1)	6.6(2.1)[a]	*F*(2,12)=4.0; *P*=0.05
HRSD	11.4(1.4)	13.6(1.3)	12.3(2.0)	12.9(1.5)	13.1(1.9)	9.6(1.5)	*F*(2,12)=2.1; *P*=0.17
Sleep items MADRS	1.3(0.8)		2.0(0.6)	3.4(0.7)		0.7(0.4)	*Z*=−1.78; *P*=0.07
Sleep items HRSD	1.8(0.8)		1.6(0.5)	2.3(0.6)		0.6(0.3)[a]	*Z*=−2.04; *P*=0.04
BDI-II total score	23.8(4.0)	23.0(2.9)	25.2(3.9)	30.3(2.9)	26.0(2.9)	22.8(3.4)	*F*(2,10)=2.7; *P*=0.11
PANAS							
Positive	20.3(2.7)	17.7(1.3)	15.3(1.5)	21.2(2.7)	18.5(3.6)	17.3(1.9)	*F*(2,10)=0.2; *P*=0.85
Negative	19.5(3.9)	22.7(2.9)	23.5(4.3)	24.5(3.3)	21.0(3.2)[b]	18.5(2.7)[a]	*F*(2,10)=5.4; *P*=0.03
Side effects	36.7(13.0)	36.3(13.0)	38.0(13.0)	47.0(14.7)	36.1(16.5)	28.3(11.9)	*F*(2,10)=1.0; *P*=0.42

SSNRI=selective serotonin–noradrenalin reuptake inhibitor; CPRS=Comprehensive Psychopathology Rating Scale; MADRS=Montgomery–Asberg Depression Rating Scale; BAS=Brief Anxiety Scale; HRSD=Hamilton Depression Rating Scale; BDI-II=Beck Depression Inventory—2nd edition; PANAS=Positive and Negative Affectivity Scale.

[a] Vs. *t*(−1 h); 0.01<*P*<0.05.

[b] Vs. *t*(−1 h); *P*<0.01. Data were missing for one patient on the self-report questionnaires.

acute administration of SSRIs. This may enhance the activation of postsynaptic 5-HT receptors.

An alternative explanation for the relief in symptoms may be that ATD counteracts the side effects of SSRIs, which may be caused by the acute rise of 5-HT (Stahl, 1998). However, there was no change on the list of physical complaints.

The present study has several limitations. Firstly, we did not systematically assess the duration of improvement beyond the first 24 h. Also, patients had been taking antidepressant medication for varying time periods. The sample was too small to investigate possible differences between patients who had not yet responded and patients who may have been treatment-resistant.

An important point concerns the generalizability of the present results, if replicable, to other serotonergically acting medications. Six patients were treated with venlafaxine and one patient with mirtazapine. The rationale to include the latter patient in the SSNRI group was that mirtazapine-treated patients in remission also respond to ATD (Delgado et al., 2002). A number of studies have shown that SSNRIs inhibit the reuptake of both serotonin and norepinephrin (NE) only at high doses (see Thase et al., 2001; Burke, 2004). Moreover, electrophysiological studies have shown that venlafaxine induces higher transporter affinity (Beique et al., 1998b), reuptake (Beique et al., 1998a, 1999), and extracellulair activity (David et al., 2003) for 5-HT compared to NE. It is expected that the effects are similar as in SSRI-treated patients.

To conclude, the present study shows that the response to ATD in currently depressed medicated patients may provide useful information about the underlying pharmacological mechanisms of action of antidepressants.

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