Serotonin, cortisol, and stress-related psychopathology

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Chapter 7

Social interaction, rather than distress or somatic complaints, is associated with low tryptophan and consequently low brain serotonin, during interferon-alpha treatment

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ABSTRACT

Objective: *Anticancer therapy with the pro-inflammatory cytokine interferon-α (IFNα) decreases tryptophan (TRP) availability to the brain which is likely to result in lower synthesis of brain serotonin. Decreased TRP availability has been associated with a variety of psychopathological symptoms. We assessed whether decreased TRP availability during IFNα therapy, is associated with symptoms of psychological distress, social interaction or somatic complaints.*

Methods: *Exploratory factor analysis was used to identify symptom clusters addressing distress, somatic complaints and social interaction based on items included in the SCL-90. The SCL-90 and central TRP availability (the plasma ratio TRP/ large neutral amino acids) were assessed at baseline, and at 4 weeks, 8 weeks and 6 months after the onset of treatment in a sample of 43 (25 male; 18 female) subjects undergoing IFNα-treatment. We used mixed models analysis to analyze the longitudinal effects of TRP availability on the three symptom clusters.*

Results: *Changes in TRP availability predicted changes in social interaction (P=0.04), but neither increasing levels of distress (P=0.35) nor of somatic complaints (P=0.35). Effects on social interaction were observed only after 4 weeks of IFNα treatment, and in the tertile of the cohort with the strongest decline in TRP availability. In this subgroup the effects were moderate to strong (standardized effect size 0.5).*

Conclusions: *Our findings suggest: 1) that decreased TRP availability leads to symptoms closely related to reactivity to environmental or interpersonal cues and 2) that social interaction might be recognized as a specific symptom rather than being incorporated in the diagnosis of psychiatric disorders*

INTRODUCTION

The recombinant cytokine interferon-α (IFNα) is used in the treatment of chronic viral hepatitis and several malignancies (135). This treatment is featured by the occurrence of a broad spectrum of side-effects, including psychopathological symptoms (291-293). These side-effects do not only negatively influence the quality of life of patients during treatment, but also the risk of non-compliance which can eventually lead to treatment discontinuation (294-296). The psychopathological side-effects can be divided into 3 types (297). The first type, somatic symptoms, includes symptoms of fever, pain, headache, weight loss and reduced appetite (293). The second type, psychological distress, includes symptoms of depression and anxiety. The incidence of these symptoms is highly variable, ranging from 0% to 50% of the treated patients (292;295;298-301). Finally, symptoms of dysfunction in social interaction, such as increased irritability, hostility, impatience, and anger, have been reported (116;297;302).

It is thought that the neuropsychiatric side-effects of IFNα therapy are associated with alterations in serotonin (5-hydroxytryptamine, 5-HT) function (137;301;303-305). The cerebral synthesis of 5-HT depends on the plasma concentration of its precursor, the essential amino acid tryptophan (TRP). Cerebral TRP is dependent on plasma levels of both tryptophan and the competitive large neutral amino acids (LNAA) for transport into the brain (87;139;141). IFNα causes enhanced degradation of TRP, but not of the other LNAA, by inducing the enzyme indoleamine 2,3-dioxygenase (IDO). This results in decreased TRP/LNAA ratios with ensuing impairment in cerebral 5-HT functioning (137-141;306).

In many cross-sectional studies TRP depletion and altered 5-HT function have been associated with mood disorders (64;65;307;308), somatic symptoms (309;310), and with hostility, irritability, and aggression (311-313), behaviors strongly influencing social interaction (314). Interestingly, in a recent study, TRP suppletion appeared to be correlated with a decrease in quarrelsome behavior (315).

In the present longitudinal observational study we investigate which of the above mentioned symptom clusters are particularly affected by a decrease in the cerebral availability of TRP during treatment with IFNα. Because many self-scoring questionnaires for depression contain ambiguous items (i.e. items reflecting all three types of complaints), this may not be the best method to use for the investigation of psychopathology in somatic diseases (292). Therefore, we tried to construct factors from the SCL-90 that consists of several of the key symptoms of the above mentioned clusters. By applying exploratory factor analysis on this multidimensional symptom score questionnaire, we could establish whether or not treatment-induced effects lead more often to some specific symptom clusters. In contrast to the existing studies in which effects on only one of the three clusters was evaluated, the present study includes all three simultaneously. As a result, it may provide evidence which of the three relevant symptom-groups, psychological distress,

somatic complaints or social interaction, are particularly associated with a decreased TRP availability and thus possibly with concomitantly low brain-5-HT function during IFNα treatment.

METHODS

Study sample

The cohort and description of patient selection has been described in detail elsewhere (316;317). In short, inclusion criteria were: between 18-75 years old and IFNα treatment being offered by their oncologist. Patient were excluded when they currently used antidepressants, antipsychotics, mood stabilizers, or corticosteroids; also excluded were patients with current abuse of illicit drugs or alcohol, patients with major depression according to DSM-IV criteria, patients suffering from severe neuropsychiatric disorders, and patients with known CNS metastases. Forty-two patients (25 m /16 f) were included; mean age was 59 years (SD 8), ranging from 36-72 years. No patient had co morbid psychiatric disorders. Four patients suffered from co morbid diabetes mellitus, 4 patients had mild coronary heart disease, one patient suffered from asthmatic bronchitis, and 3 patients had a history of malignancies (prostate cancer or breast cancer) other than those for which they were to receive IFNα treatment. Eight of the included patients were treated with pegylated IFNα (PEG-IFNα) 6 μg/kg/week subcutaneously for a period of 8 weeks, followed by a maintenance treatment of 3 μg/kg/week for a high risk melanoma. The other patients had a renal cell carcinoma and were treated with conventional IFNα with median weekly doses of 27 million units (18-27) at all time points.

In the above mentioned study, both observer-based scores (Mini-International Neuropsychiatric Interview) and self-report psychometric rating scales (Montgomery-Asberg Depression Rating Scale, Brief Anxiety Scale, Hospital Anxiety and Depression Scale, Beck Depression Inventory and SCL-90) did not show clinically relevant changes. Clinically relevant depressive states were observed in two patients. In one of these patients depression was due to metastases in the central nervous system. This patient was excluded from the analyses. Other, minor, depressive episodes were self-limited and short-lasting and associated with either episodes of flu-like symptoms common at the start of the IFNα treatment or with psychosocial events. Several alterations in laboratory parameters showed an increased degradation of peripheral TRP during treatment, but no consistent associations with various psychiatric measurements (317).

Biochemical assays

EDTA blood for determination of plasma TRP and the other LNAA (tyrosine, valine, phenylalanine, leucine and isoleucine) was obtained by veni puncture at the same time points. For practical reasons, it was not possible to obtain blood samples at fixed times or under fasting conditions. After immediate centrifugation (20 min at 2650 g) plasma was

separated and frozen at -80°C. Amino acids were determined as described (318). TRP/LNAA ratio as a measure for TRP availability to the brain was calculated by dividing 100 times the plasma concentration of TRP by the sum of the other LNAA.

Psychological assessments

Various aspects of psychological dysfunction were assessed with the Symptom Checklist-90 (SCL-90). The SCL-90 is a well validated, multidimensional self-report symptom inventory, consisting of 90 items and designed to assess various domains of psychopathology (319;320), in which a higher score on an item indicates more complaints or symptoms. The questionnaires were filled in before the start of treatment, and after 4 weeks, 8 weeks and 6 months of treatment with IFNα.

To determine the effects of changes in TRP availability on social interaction, psychological distress and somatic complaints, we factor-analyzed the following 12 items that together cover the three anticipated symptom clusters: uncontrolled temper, frequent quarrelling, feeling of not being accepted, feeling down, worrying, loss of interest, feeling tense, headache, dizziness, feeling exhausted, nausea, and dyspnea. These items were selected a priori in order to cover the three symptom clusters as well as possible. As expected, a principal components analysis on these items assessed at baseline (oblique rotation), yielded a three-factor solution together explaining 57% of variance (24% by first, 18% by second, and 15% by third factor), based on the Eigen-value >1 criterion (first factor 2.8; second 2.2; third 1.8). Because of the small sample size, we checked whether these factors were stable throughout the database. The database was randomly split and the principal component analysis was done on the two separate parts. This resulted in comparable factor compositions. The factor loadings, shown in Table 1, confirmed a distinction between social interaction, psychological distress and somatic complaints, which were virtually uncorrelated (Rfirst-second= 0.10; Rfirst-third= 0.04; Rsecond-third= 0.10). Except for the item headache (0.35 on social interaction), none of the items had secondary loadings >0.25. For the subsequent analyses, we therefore used the standardized factor scores (mean = 0; SD =1). Based on the available data, we calculated for each individual up to three change scores on each of the factors, i.e. change from baseline to four weeks, change from baseline to 8 weeks, and change from baseline to 6 months.

Data analysis

Data were analyzed using the mixed models procedure of SPSS (version 12.0) software for Windows. Mixed models analysis (321) was used to evaluate differential changes in factor scores between subjects over time as a function of changes in TRP availability from baseline. This analysis was chosen because it takes into account that data are nested within subjects (i.e. several assessments were done for each individual). A mixed models approach also takes into account the longitudinal course of these problems, as these proved to be consistently higher over time, this has resulted in an increased study power. In all analyses,

we controlled for the corresponding baseline factor score in order to evaluate the prospective effect of TRP availability on the symptom clusters. We applied a mixed models analysis using the diagonal (default) correlation structure that poses the fewest restrictions on the correlation matrix. The reason for this is that we already controlled for baseline social interaction which probably eliminates most of the correlations among the three follow up assessments. Moreover, using different assumed correlation structures results in highly comparable effect sizes for tryptophan levels. Correlations were assessed using the Spearman correlation coefficient. All the reported p-values are 2-sided and a significance level of $\alpha \leq 0.05$ was considered statistically significant.

Table 1: Factor loadings of the 12 SCL-90 items on the three factors

	Somatic	Psychological	Social
Somatic complaints			
Headache	0.67		
Dizziness	0.79		
Feeling exhausted	0.70		
Nausea	0.64		
Dyspnea	0.70		
Psychological distress			
Feeling down		0.75	
Worrying		0.83	
Loss of interest		0.67	
Feeling tense		0.79	
Social interaction			
Uncontrolled temper			0.74
Not feeling accepted			0.77
Frequent quarrelling			0.80

RESULTS

TRP concentration compared with baseline significantly decreased to 85 % (95%CI 75 – 88) at 4 weeks, 86% (95%CI 74-92) at 8 weeks, and 90% (95%CI 77-94) at 6 months. LNAA levels did not change significantly during the study period. (317). TRP/LNAA ratio compared with baseline was significantly decreased to 89% at 4 weeks (95%CI 84-92) and 87% at 8 weeks (95%CI 83-92), but was not significantly decreased at 6 months (95%CI 86-101). Total change in TRP availability ranged from 69% to 116%. Average factor scores during follow up did not differ from baseline scores. However, changes in TRP availability were significantly negatively associated with changes in factor scores on social interaction (Spearman's Rho = -.42; P<0.0001; N=77), but not with changes in factor scores on psychological distress (Spearman's Rho = -.14; P=0.24; N= 77) or on somatic complaints (Spearman's Rho = -.22; P=0.06; N=77).

Table 2: Prediction of changes in social interaction, distress and somatic complaints by changes in TRP availability

	F	P
Prediction of social interaction during follow up:		
Baseline social interaction	4.5	0.04
Change in TRP availability	4.7	0.04
Prediction of psychological distress during follow up:		
Baseline distress	40.1	<0.001
Change in TRP availability	0.9	0.35
Prediction of somatic complaints during follow up:		
Baseline somatic complaints	82.9	<0.001
Change in TRP availability	0.9	0.35

Similarly, the mixed models analyses showed that both baseline scores and the change in TRP availability predicted scores on the factor social interaction on 4- weeks, 8-weeks, and 6-months assessments. In contrast, baseline scores predicted the factor scores for psychological distress or somatic complaints at the different time points, without effect of changes in TRP availability (Table 2). When excluding one outlier (>3 SD difference from the mean of the sample) from the analysis, the results did not change. As the treatment heterogeneity of the sample might be a complicating factor, we repeated the mixed model analysis without the PEG IFNα patients. Again this did not alter the conclusion.

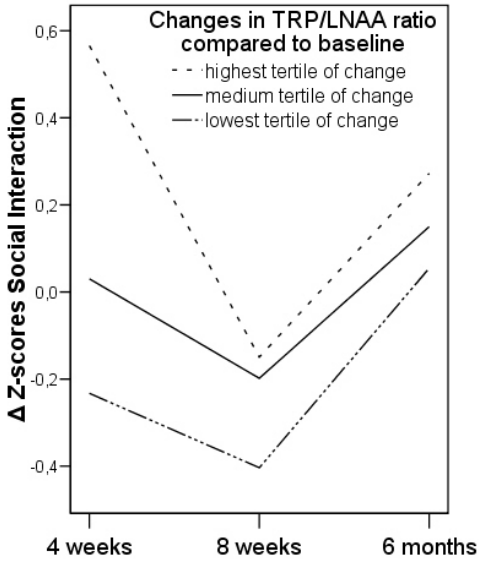

Figure 1: the magnitude of the effect of TRP availability on changes in social interaction is shown, dividing participants in tertiles based on their change in TRP availability between baseline and the subsequent 4 and 8 weeks or 6 months of treatment

Secondary analyses revealed that changes in social interaction were only seen at 4 weeks after initiation of IFNα treatment. Moreover, the effects were restricted to participants in the highest tertile of decrease in TRP availability (figure 1). The (standardized) effect size in the highest tertile at four weeks was considerable (>0.5), representing a moderate effect size (322).

DISCUSSION

We applied an exploratory factor analysis approach on SCL-90 scores to establish in which symptoms cluster IFNα-mediated effects predominate. In line with other studies (297), we distinguished 3 symptom clusters associated with the IFNα treatment referring to social interaction, distress or somatic complaints. A novel finding of the present study is that the decrease in cerebral TRP availability predicts dysfunction in social interaction, but not somatic symptoms and distress. Our study supports the idea that social interaction is associated with low TRP and thus possibly with low brain 5-HT during IFNα treatment.

Despite several papers in which depression during IFNα therapy was associated with decreases in plasma TRP, (140;323;324), we did not observe a consistent relationship between changes in TRP/LNAA ratio and psychological distress. This is in accordance with the observations of Wichers (324) Capuron (140) and co-workers. No consistent relationships between change in TRP/LNAA-ratio and changes in measures for depression were also found by Bannink and collaborators (317) who analyzed the same patient population using a different statistical approach.

There are several reasons that may account for the lack of an association between TRP/LNAA alterations and psychological distress in the present study. First, the patients in the present study had low scores on psychiatric rating scales at baseline and no history of psychiatric illnesses. The increase in depression symptoms during IFNα treatment has been mainly found in a subset of vulnerable individuals with high baseline neuroticism and low agreeableness (297). Also studies exploring the psychopathological consequences of acute TRP depletion show that increased depressive feelings occur mainly in vulnerable subjects, in particular subjects who had been successfully treated with antidepressants of the SSRI-type or had family members with depressive disorders e.g. (64;325). In most acute TRP depletion studies, no TRP induced depressive symptoms were encountered in healthy people (63;64). This suggests that only a subgroup of patients is susceptible for developing of depressive symptoms induced by changes in TRP availability. It might be that these patients were not included in our study. Indeed, most IFNα-induced depressions have been reported in patients that are treated for hepatitis C, an infectious disease that is associated with parenteral drug abusers and may thus being a more vulnerable population than the present oncological patients. Second, in the present cohort and in our previous studies (87;115;116), the low TRP condition developed gradually and persisted for a longer period of time, while in the acute TRP depletion studies low TRP levels were rapidly induced and

lasted for less than 12 hours. The gradual decrease in TRP levels observed in our patient population may also account for the lack of depressive symptoms in the present study. Finally, we used a limited number of questions from the SCL-90 and both sample size and the within-item variation between the patients were relatively small. These conditions may occlude relationships that became obvious with more variations of the tested parameters, i.e. TRP and symptoms.

We found a dysfunction in terms of social interaction to be related to a decreased availability of TRP. Although most studies on side effects of IFNα therapy have thus far focused on depression, increased levels of aggression and irritability are a well-known side effect of treatment with IFNα and have been reported previously (297;302;326). In those studies, however, plasma amino acids were not measured, so a possible relationship between psychopathology and TRP availability could not be established. Recently and consistent with our findings, increases in irritability and aggressive impulse dysregulation during IFNα treatment in patients with hepatitis C have been reported, that were significantly associated with a decrease in plasma TRP levels (115;116;326). The current findings should be considered as preliminary and should be confirmed by others. The P-value of the association between tryptophan depletion and changes in interpersonal interaction (P=0.04) may not hold after correction for multiple testing, however we feel that such a correction is not necessary given the small number of tests we conducted (3 tests) and the small sample size resulting in limited study power.

In summary, the present study confirms previous clinical observations of increased interpersonal conflicts during IFNα treatment Social problems in these severely ill medical patients will have substantial impact on the course of their illness. Such effects may be predicted by decreased TRP availability during treatment with IFNα. We suggest recognizing social interaction as a specific symptom complex related to low brain 5-HT function, rather than as an item contributing to the overall assessment of severity of psychiatric disorders, including depression. Our results may warrant testing therapeutic interventions (e.g. TRP enriched diets (315), or medication with drugs to support cerebral 5-HT functioning (305;327)) in psychopathology related with interpersonal conflicts.