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SERUM CONCENTRATIONS OF TNF-α AND ITS SOLUBLE RECEPTORS DURING PSYCHOTHERAPY IN GERMAN SOLDIERS SUFFERING FROM COMBAT-RELATED PTSD

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SUMMARY

Background: *Changes in serum concentrations of tumor necrosis factor-α (TNF-α) and its soluble receptors (sTNF-R) p55 and p75 have been shown to be associated with various psychiatric treatments.*

Subjects and methods: *Before and after treatment, serum levels of TNF-α, sTNF-R p55 and sTNF-R p75 were measured in 38 German soldiers who had been deployed abroad and suffered from combat-related post-traumatic stress disorder (PTSD). Patients were randomized either to inpatient psychotherapy (N=21) including eye movement desensitization and reprocessing (EMDR) or to outpatient clinical management (N=17). Symptoms of PTSD were measured using the Post-traumatic Stress Diagnostic Scale (PDS).*

Results: *The PDS score significantly decreased across time in both groups. Serum concentrations of TNF-α increased, while sTNF-R p55 and sTNF-R p75 levels decreased significantly. After the treatment period, we could not detect any significant difference regarding TNF-α, sTNF-R p55 or sTNF-R p75 levels between the inpatient psychotherapy group and the outpatient clinical management control group.*

Conclusions: *This relatively small clinical study suggests that specific inpatient psychotherapy but also non-specific supportive outpatient treatment for PTSD are associated with changes in the TNF-α system. This may represent an immunological effects or side effects of psychotherapy.*

Key words: *cytokines - tumor necrosis factor (TNF-α) - soluble TNF receptors - post-traumatic stress disorder - psychotherapy*

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INTRODUCTION

In recent years, cytokines, which are messenger molecules of the immune system, have received increasing attention in psychiatric research (Borovcanin et al. 2012, 2013, Maes et al. 2012, Müller et al. 2015) as they can influence various types of brain cells and their connectivity, the production and metabolism of neurotransmitters, and neuroendocrine systems (Miller et al. 2013). One cytokine that has been the subject of much scientific interest among researchers is tumor necrosis factor (TNF)-α (Berthold-Losleben & Himmerich 2008). It acts via two different receptors which can be cleaved from the surface of different types of cells and are measurable in the serum as soluble TNF-α receptors sTNF-R p55 and sTNF-R p75.

TNF-α is a glycoprotein hormone which was isolated as a soluble factor released by host cells that caused necrosis of a transplanted tumor (Carswell et al. 1975). It is released by monocytes, macrophages and other white blood cells, the endothelium, fatty tissue and several other body tissues and is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. TNF-α has been implicated in a variety of diseases, including autoimmune diseases, insulin resistance and cancer (Ghezzi & Cerami 2005).

Changes in the TNF-α system have been shown to be associated with a number of psychiatric disorders such as schizophrenia (Pandey et al. 2015, Turhan et al. 2016) and depression (Himmerich et al. 2008; Schmidt et al. 2014). However, in post-traumatic stress disorder (PTSD), results are inconsistent; some studies report increased production of TNF-α in patients suffering from PTSD (Chen et al. 2014; Lindqvist et al. 2014), others do not (Himmerich et al. 2015, 2016, Jergović et al. 2015).

In addition to psychiatric disorders *per se*, psychopharmacological treatments such as antidepressants (Kraus et al. 2002, Munzer et al. 2013), mood stabilizers (Himmerich et al. 2005, 2013) and antipsychotics (Himmerich et al. 2011; Kluge et al. 2009) have been shown to lead to changes in the TNF-α system, most often to an increase in plasma levels of TNF-α and its receptors. However, an increase of TNF-α production during therapy is not generally conceived as a favorable effect, as TNF-α is an inflammatory marker that has

been shown to be associated with psychiatric disorders such as schizophrenia (Pandey et al. 2015, Turhan et al. 2016) and depression (Berthold-Losleben & Himmerich 2008; Himmerich et al. 2008; Schmidt et al. 2014). Moreover, animal studies have shown that TNF-α production increases during stressful events such as social isolation (Krügel et al. 2014).

The effect of psychological therapies on TNF-α levels is less clear. Studies indicate that dynamic psychotherapy (Del Grande da Silva et al. 2016) and cognitive behavior therapy, but not narrative cognitive therapy (Moreira et al. 2015), may lead to decreased TNF-α production in depressed patients. To our knowledge, the effect of psychotherapy for PTSD on serum levels of TNF-α or its receptors has never been reported. To investigate this, we measured these parameters in soldiers with combat-related PTSD before and after treatment.

SUBJECTS AND METHODS

Participants

In a cross-sectional study we examined 135 male German soldiers, 38 of whom had served deployments abroad and were diagnosed with combat-related PTSD according to ICD-10 criteria as a consequence of their deployments (Himmerich et al. 2015, 2016). To be included into this study, the deployment with the event leading to PTSD had to be no more than 24 months ago.

For the present longitudinal investigation, the 38 patients with PTSD were randomly allocated to six weeks of either immediate inpatient psychotherapy (N=21) or outpatient clinical management control group (N=17). The latter patients were placed on a waiting list for later inpatient psychotherapy.

Treatment conditions

Inpatient psychotherapy comprised of 6 weeks of treatment on a specialized ward within the Department of Psychiatry, Psychotherapy and Psychotraumatology at the Bundeswehr Hospital in Berlin, Germany. The treatment package included individual eye movement desensitization and reprocessing (EMDR) treatment as well as psychotherapeutic groups, physiotherapy, occupational and art therapy. Outpatient clinical management included less structured supportive psychological therapy sessions. This group did not receive EMDR treatment. Both patient groups were allowed psychopharmacological treatments as determined by the doctor and patient, without interference.

Psychological measures

PSTD symptomatology was measured using the Post-traumatic Stress Diagnostic Scale (PDS) German version at baseline (at inpatient admission or allocation to clinical outpatient management) and after treatment (at discharge or after six weeks of outpatient treatment). The PDS was developed and validated by Foa et al. (1995) to provide a reliable self-report measure of PTSD. Its questions relate to the frequency of distressing and intrusive thoughts, posttraumatic avoidance and hyperarousal. The PDS has been shown to have high reliability and validity in measuring PTSD symptoms (McCarthy et al. 2008).

Cytokine measurement

After blood drawing at baseline and after treatment, serum probes were immediately centrifuged at 3000 rpm for 10 min. The supernatant was aliquoted and stored in non-absorbing polypropylene tubes of 300 µl. Probes were shock-frozen in liquid nitrogen and stored in freezers at -80 ºC until further measurement. TNF-α and its soluble receptors sTNF-R p55 and p75 were measured in the serum using a Bio-Plex Pro™ human cytokine immunoassay from Bio Rad, Germany. An implausible outlier of TNF-α>100 pg/ml (n=1) was excluded from the analysis.

Statistics

Repeated measures ANOVAs (group: inpatient psychotherapy; outpatient control) x (time: baseline; post-treatment) were used to examine effects of treatment condition on the dependent measures of PDS and cytokine levels. Concurrent medication was dichotomized into two groups, those receiving antidepressants and those receiving homeopathic or no medication, and analyzed by repeated measures ANOVAs (Medication: on antidepressants; not on antidepressants) x (time: baseline; post-treatment) for TNF-α and its soluble receptors. All statistical tests were performed using SPSS 21. As this was a pilot study, we accepted an uncorrected p-value of $p<0.05$ as an indicator of statistical significance.

Ethics

The study was approved by the local ethics committee (Ethikausschuss Charité, application number: EA1/270/11).

RESULTS

Psychosocial group characteristics

Mean age of the whole study sample (including the inpatient and outpatient treatment groups) was 28.5 (±5.6) years, and the average body mass index (BMI) was 27.3 (±3.4) kg/m^2. Age, BMI and PDS score are shown separately for each treatment group in Table 1. At baseline, the whole sample showed a PDS score of 31.5 (±10.5) and after treatment a score of 28.1 (±13.2), demonstrating a significant decrease over time [$F(1, 28)=6.39$, $p<0.05$]. There was no significant main effect of group [$F(1, 28)<1$, n.s.] or group x time interaction.

Table 1. Mean and standard deviation (SD) of the descriptive variables age and body mass index (BMI) as well as the outcome parameters Post-traumatic Stress Diagnostic Scale (PDS) score and serum concentrations of tumor necrosis factor-α (TNF-α) and its soluble receptors (sTNF-R) p55 and p75 separately for both treatment groups at baseline and after treatment

		Inpatient psychotherapy (N=21)				Outpatient clinical management (N=17)			
Descriptive Variables		*Mean*	*SD*			*Mean*	*SD*		
	Age [years]	28.0	7.62			28.8	3.40		
	BMI [kg/m^2]	27.8	2.03			26.9	4.13		
		Baseline		After treatment		Baseline		After treatment	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Outcome Parameters	PDS score	29.0	12.0	24.8	12.9	33.6	8.9	30.9	13.2
	TNF-α [pg/mL]	5.2	4.48	17.6	6.91	7.4	5.16	18.9	6.84
	sTNF-R p55 [pg/mL]	405.2	110.7	356.0	114.5	400.8	137.8	319.4	116.9
	sTNF-R p75 [pg/mL]	1412.0	439.8	1212	359.4	1250.0	375.2	1154	471.7

Regarding the whole group, there was a significant increase in TNF-α serum concentration ($p<0.01$), but a significant decrease of sTNF-R p55 ($p<0.05$) and sTNF-R p75 ($p<0.05$) levels during the treatment period. Significant group differences in TNF-α parameters (inpatient vs. outpatient therapy) were not detected

Parameters of the TNF-α system

Table 1 also shows the serum concentrations of TNF-α and its soluble receptors sTNF-R p55 and sTNF-R p75 separately for both treatment groups. Regarding the whole group, there was a significant increase over time with regard to TNF-α [$F(1, 29)=81.03$, $p<0.001$], contrasting with a significant decrease to its receptors sTNF-R p55 [$F(1, 31)=8.94$, $p<0.01$] and sTNF-R p75 [$F(1, 28)=4.82$, $p<0.05$]. No significant main effect of group or group x time interaction was detected for TNF-α, sTNF-R p55 and sTNF-R p75 serum concentrations [all: $F(1, 28\text{-}31)<1$, n.s.].

Influence of antidepressant medication

We compared patients taking antidepressants (N=16) with those using homeopathic remedies or no psychotropic medication. No statistically significant differences were found for TNF-α, sTNF-R p55 and sTNF-R p75. In a consecutive ANCOVA controlling for medication all previously detected statistical effects remained significant: TNF-α [$F(1, 28)=10.81$, $p<0.01$]; sTNF-R p55 [$F(1, 29)=5.41$, $p<0.05$] and sTNF-R p75 [$F(1, 26)=5.10$, $p<0.05$]. We also calculated spearman rank correlations between the changes in the TNF-α system and the PDS scores. No statistically significant correlations between decrease in PDS score and changes in the parameters of the TNF-α system were found.

DISCUSSION

Both treatment groups showed a significant decrease in PTSD symptoms after treatment as measured by the PDS score. In addition, whereas TNF-α concentrations increased, sTNF-R p55 and sTNF-R p75 levels decreased significantly over time in the whole study sample. To our knowledge, this is the first study investigating possible changes within the TNF-α system during psychological treatment for PTSD. Therefore, the present investigation suggests that clinical improvement following PTSD treatment might influence the production or release of TNF-α and sTNF-Rs.

Changes of TNF-α, sTNF-R p55 and sTNF-R p75 levels during psychological treatment could theoretically be due to a degree of recovery from PTSD or represent an effect or side effect of psychotherapy. However, our previous study did neither show any correlation between serum levels of TNF-α, sTNF-R p55 or sTNF-R p75 and the PDS scores in this patient sample (Himmerich et al. 2015) nor any statistically significant difference of TNF-α, sTNF-R p55 or sTNF-R p75 serum levels of soldiers with PTSD compared to those without PTSD (Himmerich et al. 2016). Consistent with these findings, in the present study we did not find any statistically significant association between the decrease in the PDS score and the changes in the parameters of the TNF-α system. Therefore, it seems unlikely that TNF-α, sTNF-R p55 or sTNF-R p75 levels changed as a result of an improvement of PTSD symptoms.

As animal studies have shown that TNF-α production increases during stressful events (Krügel et al. 2014), one consideration may be that EMDR therapy, which includes imagination of a trauma, or being allocated to outpatient clinical management, instead of a perceived more favorable specific psychological treatment for PTSD (e.g. inpatient psychotherapy), could also lead to stress. Therefore, an increase of TNF-α production or release could be a side effect of psychotherapy or a result of patient disappointment.

From a psychopharmacological perspective, the increase of TNF-α production we observed is not surprising, since a number of effective psychopharmacological drugs, such as mirtazapine (Kraus et al. 2002), carbamazepine and lithium (Himmerich et al. 2005), clozapine and olanzapine (Kluge et al. 2009), have also been shown to lead to changes in the TNF-α system.

TNF-α has been implicated in the development of autoimmune diseases (Ghezzi & Cerami 2005). For example, its elevation during lithium therapy has been thought to play a role in the appearance or exacerbation of psoriasis or hypothyroidism, a side effect of lithium therapy (Petersein et al. 2015). Increased production of TNF-α during lithium therapy is seen as an advantage for patients suffering from human immunodeficiency virus (HIV) infection (Petersein et al. 2015). However, the effects of psychotherapy on the cytokine system and their consequences for the course of infectious diseases and autoimmune disorders have scarcely been investigated. While this may be an interesting question to arise from the results of the present study, our data should not be used to draw far-reaching conclusions in terms of a direct effect of psychotherapy on the immune system.

The changes in the TNF-α system observed could also be a consequence of psychotherapy leading to the intended effects of treatment, as short-term stress and activation of physiological parameters during psychotherapy could result in long-term improvement. This idea has already been considered in other areas of psychotherapy in terms of changes in cortisol production during stress. For example, in eating disorders, mirror confrontation leads to an increase in skin conductance and saliva cortisol concentration (Vocks et al. 2007). Such an increase in saliva cortisol has also been reported during in-vivo exposure of agoraphobic patients (Schumacher et al. 2014). Furthermore, basic research in humans and animals has shown that cortisol can enhance memory consolidation of new information, but impair memory retrieval of already stored information (de Quervain et al. 2009). On the basis of these known effects on memory processes, it has been proposed that cortisol enhances exposure therapy through two mechanisms: 1) cortisol-induced reduction of memory retrieval: an aversive cue is no longer followed by the usual, full-blown retrieval of fear memory and; 2) cortisol is known to enhance memory consolidation of new information and is assumed to enhance the storage of corrective experiences (de Quervain et al. 2011, Lass-Hennemann & Michael 2014). Therefore, cytokine activation during psychotherapy could also theoretically have favorable effects which are yet to be determined.

However, it may be that not psychotherapy itself, but rather behavioural consequences of psychotherapy or the behavioural changes associated with returning home after deployment have caused the observed alterations within the TNF-α system. Such changes could be due to nicotine or alcohol consumption, lifestyle, physical activity or diet. Unfortunately, we did not gather data on these factors longitudinally. Furthermore, the simple change of location and the consecutive adaptations within the immune system should also be taken into account when interpreting the present data.

The TNF-α parameters did not significantly differ between the inpatient psychotherapy group and the outpatient clinical management group. Therefore, inpatient psychotherapy (including EMDR) does not seem to exert a specific influence on TNF-α, sTNF-R p55 and sTNF-R p75 serum concentrations. Rather, as changes were observed in both treatment groups, a non-specific effect of psychotherapy could have contributed. This is supported by studies in depressed patients showing that cognitive behavior therapy (Moreina et al. 2015) as well as dynamic psychotherapy (Del Grande da Silva et al. 2016) lead to changes in TNF-α production. Thus, psychotherapy may influence the TNF-α system, independently of the specific diagnosis or the specific psychotherapeutic approach. Given that several other types of psychiatric treatment including psychopharmacological drugs (Himmerich et al. 2005, Kraus et al. 2002), relaxation training (Koh et al. 2008) and electroconvulsive therapy (Rotter et al. 2013) modulate the TNF-α system, an influence of psychotherapy on these parameters is also conceivable. However, in the current study, we cannot rule out that the changes in TNF-α, sTNF-R p55 and sTNF-R p75 levels are a pure effect of time after deployment abroad. To investigate this thoroughly would require a control group suffering from combat-related PTSD receiving no treatment, which would have been ethically unjustifiable. Further longitudinal research into cytokine responses in relation to various stressors, emergence of disorders and during periods of treatment would likely be informative.

Even though certain antidepressants are known to influence cytokine production (Kraus et al. 2002), the use of antidepressants did not influence TNF-α, sTNF-R p55 and sTNF-R p75 levels in our sample. As the patients in our sample used different types of antidepressants, we could only compare patients taking antidepressants with those using no antidepressant medication. As some antidepressants, such as venlafaxine (Kraus et al. 2002), may not influence TNF-α, sTNF-R p55 and sTNF-R p75 levels, our investigation is not suitable to study the influence of antidepressants on cytokine production specifically.

A further limitation of this study is the small sample size of 38 patients in total, with 21 in the inpatient psychotherapy group. However, psychopharmacological agents, such as the antidepressant mirtazapine, the mood stabilizers lithium and carbamazepine and the antipsychotics olanzapine and clozapine, have been reported to influence the TNF-α system in studies with a comparable or smaller sample size (Kraus et al. 2002, Himmerich et al. 2005, Kluge et al. 2009).

Another limitation of the present investigation is that sTNF-R p55 or sTNF-R p75 serum levels in these soldiers were not measured prior to deployment abroad. Such a longitudinal study design starting prior to deployment abroad would have enabled more specific conclusions about a possible connection between PTSD and parameters of the TNF-α system.

In addition, in the present study, we did not attempt to detect feigned PTSD or PTSD symptom exaggera-

tion, in a standardized way, although measures for detecting malingering, such as specific scales of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), are available (Efendov et al. 2008). This issue might be specifically pertinent in soldiers because of eligibility for a state pension or other benefits if their PTSD is determined to be combat-related and treatment-resistant. Therefore, one could question the initial PTSD diagnosis of these patients. However, the patients were assessed by an experienced military psychiatrist and obvious malingering would have obviated their inclusion in the study.

CONCLUSIONS

To our knowledge, we performed the first study investigating the effect of psychiatric therapy and specifically inpatient psychotherapy including EMDR on serum levels of TNF-α, sTNF-R p55 or sTNF-R p75 in PTSD patients. The specific inpatient psychotherapy but also non-specific outpatient clinical management treatment reduced PTSD symptoms as measured by the PDS score and altered TNF-α, sTNF-R p55 and sTNF-R p75 concentrations. It seems to be most likely that these changes are attributable to non-specific psychotherapeutic effects or side effects. From a methodological view, further confirmatory studies should incorporate a longitudinal design starting at the time before the deployment abroad, include a control group without any treatment, have a larger sample size and should try to detect feigned PTSD as well as PTSD symptom exaggeration.

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Conflict of interest: None to declare.

Contribution of individual authors:

Hubertus Himmerich, Gerd D. Willmund, Peter Zimmermann, Antje H. Bühler & Ulrich Wesemann designed the study;
Gerd D. Willmund, Peter Zimmermann, Jörg-Egbert Wolf, Antje H. Bühler, Lesca M. Holdt & Ulrich Wesemann performed the study;
Lesca M. Holdt & Daniel Teupser measured TNF-α and sTNF-R concentrations;
Hubertus Himmerich, Gerd D. Willmund, Antje H. Bühler & Ulrich Wesemann conducted the statistical analysis;
all authors discussed the results and drafted the manuscript;
Hubertus Himmerich, Gerd D. Willmund, Kenneth C. Kirkby, Bethan Dalton & Ulrich Wesemann wrote the paper.

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