The Endocrine-Immune Interactions in Posttraumatic Stress Disorder

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Introduction

Immune response is modulated by positive and negative signalling from neuroendocrine and other bodily tissues. A complex and dynamic molecular network that regulate interactions are influenced by internal and external signals or stressors. Therefore, the stress response can be considered as a study model for neuroendocrine-immune interactions. Distinct profile of hypothalamic-pituitary-adrenocortical (HPA) axis, manifested by low cortisol level and increased number of glucocorticoid receptors (GR), is considered to be characteristic of posttraumatic stress disorder (PTSD). This is congruent with compromised cellular immune response reported in chronic stress. The findings mainly rely on studies performed decades following exposure to trauma.

Objective

The purpose of this study was to evaluate the effect of combat-associated traumatic experience on hormonal and immune responses in war veterans with PTSD diagnosed by DSM-IV within 8 years after exposure to trauma.

Subjects and methods

Participants were 39 PTSD sufferers aged 25-50 (mean = 34) years and 37 age matched civilian controls. Serum hormone (cortisol, prolactin, T3, T4) and cytokine (IL6, TNF-alpha) levels were determined by radio- and enzyme immunoassays respectively. The total lymphocyte count and the proportions of total T ($CD3^+$), B ($CD20^+$) and NK ($CD3^-CD16^+56^+$) cells, helper ($CD3^+CD4^+$) and cytotoxic ($CD3^+CD8^+$) T lymphocytes, CD4 memory ($CD4^+CD45RO^+$), and activated B ($CD20^+CD23^+$) cell subpopulations were determined by flow cytometry. Polymorphonuclear phagocytic (ingestion, digestion, ADCC) functions, and NK cell activity were measured by ^{51}Cr-release assays. Glucocorticoid receptor expression in lymphocytes and NK cells was determined by flow cytometry after surface phenotyping followed by intracellular staining of GR with alpha-GR FITC-labeled MoAb.

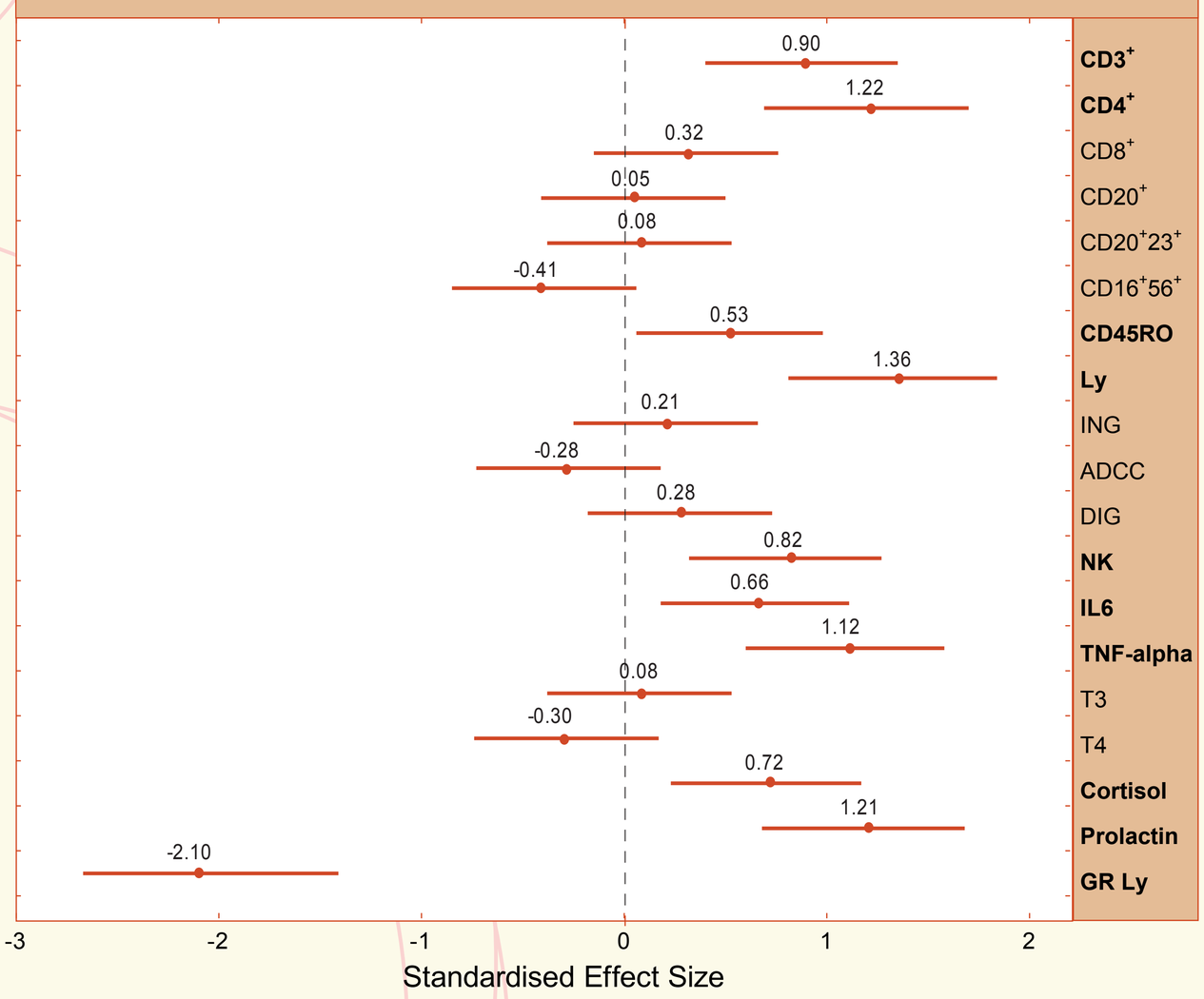
Results

	PTSD (n = 39)		Healthy Controls (n = 37)		F df (1,74)	p* adjusted
	Median	16. - 84. Pct	Median	16. - 84. Pct		
$CD3^+$	**73.0**	**66.3-82.7**	**67.0**	**57.0-74.0**	**17.0**	**< 0.001**
$CD4^{+\,T}$	**46.8**	**39.9-53.8**	**37.0**	**26.1-46.6**	**30.6**	**< 0.001**
$CD8^{+\,T}$	25.6	21.1-32.3	23.0	18.8-32.9	2.0	> 0.05
$CD20^{+\,T}$	12.1	6.8-18.3	11.0	9.0-14.0	0.03	> 0.05
$CD20^+23^{+\,T}$	5.7	3.3-10.5	6.0	4.0-8.0	0.4	> 0.05
$CD16^+56^{+\,T}$	19.7	11.4-31.2	24.2	12.1-30.3	2.6	> 0.05
CD45RO	**53.0**	**41.3-65.0**	**49.0**	**36.0-58.0**	**5.7**	**< 0.05**
Ly^T	**3552.2**	**2462.5- 5015.7**	**1723.9**	**1362.3-3557.6**	**39.1**	**< 0.001**
ING	41.0	21.4-65.6	35.0	21.0-56.0	1.1	> 0.05
$ADCC^T$	44.3	17.9-78.0	53.6	28.6-79.8	1.1	> 0.05
DIG	34.0	18.4-56.7	31.0	15.0-45.9	1.8	> 0.05
NK	**49.0**	**30.4-63.0**	**33.0**	**21.0-53.9**	**13.8**	**< 0.01**
$IL6^T$	**11.2**	**6.6-38.7**	**7.0**	**5.4-16.6**	**9.6**	**< 0.01**
TNF-alpha	**17.9**	**2.5-21.9**	**9.4**	**0.3-18.8**	**2.9§**	**< 0.01**
T3	2.0	1.5-2.5	2.0	1.5-2.3	0.01	> 0.05
T4	91.2	67.8-123.4	97.3	84.1-114.4	1.8	> 0.05
Cortisol	**17.0**	**14.0-22.5**	**14.8**	**11.5-17.9**	**10.8**	**< 0.01**
$Prolactin^T$	**10.5**	**6.3-34.1**	**5.7**	**3.5-10.8**	**26.4**	**< 0.001**
GR Ly	**30.4**	**24.8-38.8**	**49.0**	**39.2-59.1**	**88.2**	**< 0.001**

[T] Variables that have been transformed (Box-Cox transformation).
[§] Adjusted Z value from Mann-Whitney U test.
* Adjusted significance level for false discovery rate (FDR).

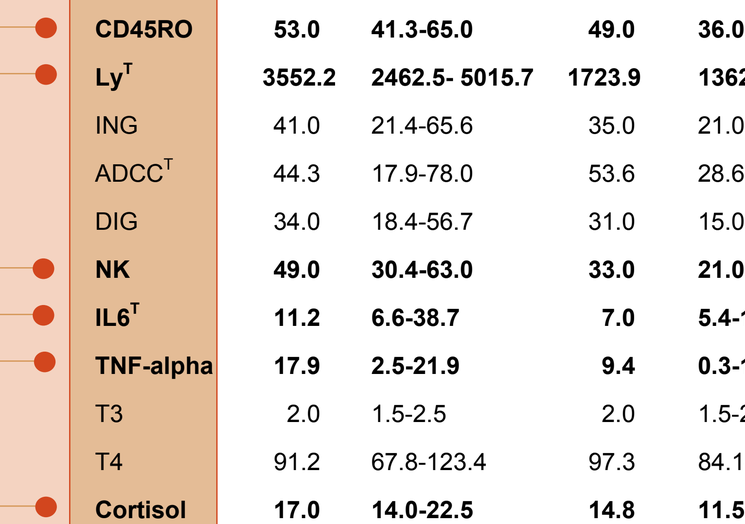
Abbreviations: ADCC – antibody depended cell cytotoxicity; DIG – digestion; GR Ly – lymphocyte glucocorticoid receptor expression; ING – ingestion; Ly – lymphocytes number; Pct – percentile; T3,T4 – thyroid hormones

Figure 1



Effect size calculation was based on Mann Whitney U statistics (described in: Newcombe RG, Statist med, 2006)

Figure 2



Correlation between hormonal variables and phenotypic canonical variate
T4 - 0.361 (13)§
Cortisol 0.122
Prolactin 0.557 (31)

Correlation between phenotype variables and hormonal canonical variate
CD3+ 0.243
CD20+ - 0.190
CD16+56+ - 0.194
Ly 0.538 (29)

Figure 3

Correlation between hormonal variables and functional canonical variate
T4 0.131
Cortisol - 0.069
Prolactin - 0.492 (24)

Correlation between functional variables and hormonal canonical variate
ING - 0.174
ADCC 0.010
DIG - 0.031
NK - 0.409 (17)
IL6 0.008

* Axes are numerated according to canonical scores for given set of variables;
§ number in brackets represent % variance explained

Conclusions

Although PTSD is considered to be associated with the immunosupression, our results of higher circulating lymphocyte count, as well as increased percentages of CD3, CD4 and CD45RO cells, indicate activation of the immune system. This was further supported by the enhanced NK cell activity and the higher levels of proinflammatory cytokines.

Opposite to the most common finding of lower cortisol level and higher receptor expression found in PTSD, enhanced cortisol secretion observed in this study was compensated with the lower glucocorticoid receptor expression on lymphocytes.

Canonical correlation analysis revealed significant correlation between the hormones and the lymphocyte number and NK cell activity, suggesting their vulnerability to the hormonal changes during stress response.

Except being elevated in PTSD patients, prolactin showed rather strong relationship with the phenotype and was also inversely related to the immune function. Exact role of prolactin in the modulation of immune system during stress response, especially PTSD, needs to be elucidated.

All of the observed changes occurred within 8 years from the initial traumatic event. Discrepancies with the other reports may have arisen due to the differences in duration of PTSD.