International Journal of Biotechnology and Biochemistry.
ISSN 0973-2691 Volume 9, Number 2 (2013) pp. 231-243

http://www.ripublication.com/ijbb.htm

Association of Hormonal Axes Changes with Oxidative Stress in Posttraumatic Stress Disorder for Iraqi Terror Attack Victims

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Abstract

There is accumulating evidence for a link between posttraumatic stress disorder (PTSD) and reduced health status. The present study aimed to investigate theassociation of hormonal axes changes with oxidative stress in PTSD patients and control group.

Ninety three subjects (82 males, 11 females) witnessed on explosion occurred at 10thJune 2010 at the exit of public employees in the State Company for Textile Industries in Hilla city of Iraq, as well as fifty subjects (35 males, 15 females) apparently healthy controls as a control groups. Participants were grouped to four groups according to PTSD Checklist (PCL) scores. Adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), total thyroxine, (T_4) total triiodothyronine (T_3) and T_3/ T_4 ratio, were determined using ELISA. Superoxide dismutase (SOD) catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), albumin and lipid peroxidation were determined using spectrophotometric methods.

$T_3$was found to be significantly increased in high PCL scores group, whereas ACTH, TSH, T_4, T_3, T_3/ T_4 ratio, SOD, GPx, and MDA, found to be insignificantly increase in the present study, whereasCAT, GSH, and albumin

showed an insignificant decreased in all groups of PTSD patients, when compared to control group. Cortisol levels were significantly decreased in high PCL symptoms scores groups of PTSD patients, when compared to control group. In conclusion, results may indicate an involvement of mild oxidative stress in the pathogenesis of PTSD due to the dysregulation of hypothalamic-pituitary-adrenal (HPA) axis, and active hypothalamic-pituitary-thyroid (HPT) axis.

Keywords: HPA, HPT, oxidative stress, PTSD, hormone, thyroid.

Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder involving both somatic and psychological symptoms that occur as a consequence to severe trauma [1]. PTSD was defined in Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) as the development of symptoms next exposure to an extreme traumatic event[2]. The most common types of traumatic event reported that may lead to PTSD are witnessing someone being injured or killed, being involved in a natural disaster, and being involved in a life-threatening accident [3].

The symptoms of PTSD described by DSM-IV involve: re-experience of the trauma, avoidance of thoughts and/or places associated with the traumatic event, enhanced vigilance and hyperarousal, sleep disturbances, and emotional numbing. These symptoms should be continued for more than 1 month [4]. Symptoms that have been present for 1 to 3 months are termed acute, whereas those that persist beyond 3 months are considered chronic. The development of symptoms 6 months or more after the trauma is termed delayed onset [2].

The lifetime prevalence of PTSD in adult Americans is reported to be 6. 8% and the conditional risk for PTSD following trauma exposure ranges from 5 to 31% with interpersonal and combat trauma associated with relatively greater risk. Although an estimated 75% of the population has experienced a criterion A of DSM-IV traumatic event, only a minority of those individuals subsequently develop PTSD [5].

PTSD symptoms are currently postulated to reflect the pathological changes in neurobiological stress-response systems, or failure of neurobiological systems to recover from, or adapt to extreme stressors [6]. Some of neurobiological investigations in PTSD have concentrating on stress-regulating neuroendocrine systems, such as for instance the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary- thyroid (HPT) axes [7, 8]. However, finding on HPA changes have not been consistent [8].

Reactive oxygen species (ROS) or free radicals which produce oxidative stress result from metabolic and physiological processes, and harmful oxidative reactions that may occur in organisms and are removed via enzymatic and non-enzymatic antioxidative mechanisms. The increases in oxidants and decreases in antioxidants cannot be avoided, and the oxidative/antioxidative balance shifts towards the oxidative stress in more than 100 types of diseases [9, 10].

Clinical and experimental studies have shown that oxidative stress participate in many psychiatric disorder which may lead to neuronal loss in cerebral ischemia and haemorrhage, also it may be involved in degeneration of neurons in normal aging [11], epilepsy [12], Parkinson's disease [13], Alzheimer's disease [14], and possibly in schizophrenia which is considered as a major psychiatric disorder. [15].

This study is designed to investigate theassociation of hormonal axes changes with oxidative stress in PTSD patients and control group. To our knowledge, no previous study concerning this issue has carried out in Iraqi population.

Study Area

Biochemistry and Psychiatry.

Material and Methods

Patients

Ninety three subjects (82 males, 11 females) who were witnessed on explosion occurred at 10th June 2010 at the exit of public employees in the State Company for Textile Industries in Hilla city of Iraq. All these subjects are employees in the State Company for Textile Industries, as well as fifty subjects work in the State Company for Textile Industries (35 males, 15 females) who are apparently healthy were used as control groups.

Diagnosis of patients was done according to trained psychologist raters according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV by use PTSD Checklist (PCL) scores self-reported. The PCL is a self-report questionnaire consisting of 17 DSM-IV PTSD symptoms. They are rated on a six-point scale ranging from “not at all” to “extremely. ” Items are added to obtain a total score. The higher the score, the more symptoms are present. A cutoff score of 50 was used for this analysis to indicate PTSD status [16].

Participants were categorized to four groups according to PCL scores: ≥50 (A), 26-49 (B), ≤ 25 (C), and control group (D).

Blood Collection

Five milliliters of overnight fasting blood were drawn at 8:00-8:30 am and allowed to clot for 15 minutes. Serum was obtained by centrifuging for 10 minutes at a relative centrifugal force (RCF) 2000 x g.

Methods

Adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), total thyroxine (T_4) and total triiodothyronine (T_3) were determined using ELISA technique according to manufacturer's manuals.

Superoxide dismutase (SOD) activity was determined by use a simple and rapid method [17], based on the ability of the enzyme to inhibit the autoxidation of pyrogallol. The autoxidation of pyrogallol in the presence of EDTA in the pH 8. 2 is 50%**.** SOD activities were expressed as units/ml. one unit of SOD activity being

defined as amount of enzyme required to cause 50% inhibition of pyrogallol autoxidation [17].

Thecatalase (CAT) activityassay performedusing spectrophotometric determination of hydrogen peroxide which form stable complex with ammonium molybdate that absorbs at 405 nm [18]. One unit CAT decomposes 1 µmole of hydrogen peroxide/ l minute under assay conditions. CAT activities were expressed as kilo unit per liter (kU/l)

Total glutathione peroxidase (GPx) activity was measured by the reaction of cumenehydroperoxide with glutathione (GSH) as the reducing substrate to form yellow color that is absorbed at 412 nm. [19]

Serum glutathione GSH was determined by using a modified procedure utilizing Ellman's reagent. 5, 5´-Dithiobis (2-nitrobenzoic acid) (DTNB) is a disulfide chromogen that is readily reduced by sulfhydryl group of GSH to an intensely yellow compound. The absorbance of the reduced chromogen is measured at 412nm and is directly proportional to the GSH concentration. [20]

Serum albumin was determined according to the commercially available kits (BIOLABO SA, France), based on bromocresol green method. [21].

Serum malondialdehyde (MDA) was determined by the colorimetric thiobarbituric acid (TBA) method. Lipid peroxides break down to form MDA under acidic and heating conditions. The latter compound reacts with TBA to form pink complexes absorb maximally at 532 nm [22].

Statistical analysis

All values were expressed as mean ± standard deviation (SD). Student's t-test was used to estimate differences between the groups, and the differences were considered significant when the probability (P) was $P< 0.05$.

Analysis of variance (ANOVA) was used to observe the difference among the groups.

The correlation between two variables was determined using Pearsons's correlation coefficients with 95% confidence interval.

Results

The ages of patient with PTSD and healthy controls subject to present study are shown in Table 1.

There are insignificant differences in mean age of patients with PTSD when compared with control group, and ANOVA showed no differences among patients groups.

Table 2 shows the clinical variables of PCL symptoms scores and the four subscales of patients with PTSD.

ANOVA shows highly significant difference in PCL symptoms scores with ($P<0.000$) between group A and both of groups B and C in each of clinical variables of symptoms: reexperience, avoidance, hyperarousal and duration.

ACTH levels in the present study found to be insignificantly increased in PTSD patients groups when compared with healthy control group, and ANOVA showsinsignificant differences among patients groups. ACTH levels increased with

severity of PTSD. Whereas, cortisol levels found to be significantly decreased in group A and B, but insignificantly decreased in group C of PTSD patients when compared with healthy control group. Cortisol levels were decreased with severity of PTSD. As a consequence, ACTH/Corisol ratios were insignificantly increased in PTSD patients groups when compared with healthy control group, and ANOVA revealsinsignificant differences among patients groups. ACTH/Corisol ratios were increased with severity of PTSD, as shown in Table 3.

T_3 levels in high PCL score (group A) found to be significantly increased, whereas TSH, thyroid hormones T_4 and T_3, in the remains group (B and C) and T_3/T_4 ratio in the present study found to be insignificantly increased in PTSD patients groups, when compared with healthy control group, . ANOVA showed insignificant differences among patients groups. TSH, T_4, T_3andT_3/T_4 ratiolevels were increased with severity of PTSD as shown in Table 4.

The antioxidant enzymes activities, SOD, GPx, and MDA, found to be insignificantly increased in the present study, whereas, the antioxidant enzyme activity CAT, non-enzymatic antioxidant GSH and albumin were insignificantly decreased in all groups of PTSD patients, when compared to control group, as shown in Table 5.

Table 1 Age of Patients with PTSD and Healthy Controls.

	Group A	**Group B**	**Group C**	**Group D**
Age Mean (years)	46. 78	44. 31	44	43. 60
± SD	6. 28	5. 64	5. 16	7. 28
P	0. 11	0. 69	0. 81	
95% C. I.	37-57	35-61	36-55	34-58

Where SD = standard deviation, P = probability, C. I. = confidence interval.

Table 2: Clinical variables of PCL symptoms scores and the four subscales of patients with PTSD.

	Group A		**Group B**		**Group C**	
	Mean	±SD	Mean	±SD	Mean	±SD
Total Scores (1-95)	63. 26	8. 43	36. 09	6. 81	14. 67	6. 18
Reexperience (0-20)	14. 26	3. 64	8. 87	3. 14	3. 62	2. 03
Avoidance (0-35)	20. 17	6. 21	11. 36	4. 34	4. 35	2. 72
Hyperarousal (0-30)	22. 39	3. 67	13. 42	4. 87	6. 02	4. 59
Duration (0-10)	6. 72	2. 74	2. 42	1. 88	0. 69	1. 01

Table 3 Serum ACTH, cortisol levels and ACTH/Corisol ratios of PTSD patients and healthy control.

	Group A	Group B	Group C	Group D
Mean ACTH (pg/ml)	25. 79	24. 86	24. 01	23. 70
± SD	13. 01	16. 79	17. 05	10. 29
P	0. 52	0. 73	0. 92	
95% C. I.	20. 03-31. 54	18. 81-30. 92	18. 32-29. 7	20. 34-27. 01
Mean Cortisol (µg/dl)	9. 62	9. 90	11. 28	12. 53
± SD	3. 43	3. 93	5. 82	5. 06
P	0. 012	0. 019	0. 33	
95% C. I.	8. 11-11. 14	8. 51-11. 3	9. 34-13. 23	10. 61-14. 14
Mean ACTH/Cortisol ratio	2. 90	2. 60	2. 30	2. 28
± SD	1. 32	1. 63	1. 54	1. 47
P	0. 10	0. 40	0. 96	
95% C. I.	2. 31-3. 48	2. 01-3. 19	1. 78-2. 81	1. 79-2. 83

Table 4 TSH levels in PTSD patients and healthy control.

	Group A	Group B	Group C	Group D
Mean TSH (µIU/ml)	1. 24	1. 20	1. 10	1. 14
± SD	0. 45	0. 89	0. 82	0. 91
P	0. 30	0. 81	0. 81	
95% C. I.	1. 03-1. 44	0. 87-1. 52	0. 82-1. 37	0. 84-1. 45
Mean T_4 (µg/dl)	9. 06	8. 78	8. 67	8. 42
± SD	1. 61	2. 45	2. 15	1. 95
P	0. 089	0. 509	0. 606	
95% C. I.	8. 34-9. 77	7. 89-9. 66	7. 94-9. 4	7. 76-9. 06
Mean T_3 (ng/ml)	0. 95	0. 91	0. 87	0. 84
± SD	0. 18	0. 29	0. 26	0. 20
P	0. 018	0. 23	0. 55	
95% C. I.	0. 873-1. 03	0. 81-1. 02	0. 78-0. 96	0. 77-0. 91
Mean T_3/T_4 ratio $X10^{-3}$	10. 683	10. 681	10. 604	10. 323
± SD	1. 826	2. 658	3. 827	2. 752
P	0. 543	0. 58	0. 718	
95% C. I.	9. 83-11. 82	9. 72-11. 85	9. 53-11. 63	9. 39-11. 35

Table 5 Oxidant and antioxidant parameters in PTSD patients and healthy control.

Group		SOD (U/ml)	CAT (kU/l)	GPx (U/l)	GSH (µM)	MDA (µM)	Albumin (g/dl)
A	**Mean**	2. 81	26. 07	244. 46	23. 76	6. 71	**4. 29**
	SD	0. 38	6. 97	51. 21	9. 79	1. 70	**0. 43**
	P	0. 056	0. 23	0. 089	0. 165	0. 063	**0. 16**
	95 % C. I.	2. 65-2. 98	22. 98-29. 15	221. 81-267. 1	19. 43-28. 09	5. 96-7. 46	**4. 10-4. 48**
B	**Mean**	2. 78	26. 46	240. 66	24. 13	6. 20	**4. 57**
	SD	0. 35	9. 97	52. 73	12. 61	3. 10	**0. 57**
	P	0. 064	0. 38	0. 112	0. 219	0. 42	**0. 41**
	95 % C. I.	2. 66-2. 91	22. 92-30. 00	221. 96-259. 36	19. 66-28. 61	5. 10-7. 30	**4. 37-4. 77**
C	**Mean**	2. 74	27. 781	234. 56	25. 58	5. 76	**4. 45**
	SD	0. 43	7. 85	83. 62	13. 78	3. 46	**0. 43**
	P	0. 200	0. 78	0. 35	0. 466	0. 86	**0. 91**
	95 % C. I.	2. 59-2. 88	25. 16-30. 40	206. 68-262. 44	20. 98-30. 18	4. 61-6. 92	**4. 31-4. 60**
Control	**Mean**	2. 61	28. 24	218. 60	27. 76	5. 647	**4. 46**
D	**SD**	0. 43	6. 71	66. 17	12. 56	2. 83	**0. 52**
	95 % C. I.	2. 47-2. 75	25. 99-30. 24	196. 94-239. 18	23. 45-31. 32	4. 87-6. 62	**4. 30-4. 63**

Discussion

One of the main findings of present study isthe association of relatively high 8:00 a. m. basal ACTH levels with low 8:00 a. m. basal cortisol levels in PTSD patients in comparison with healthy subjects. This finding is in agreement with the studies of Yehuda et al. for ACTH andKanter et al. for cortisol, [23, 24].

Yehuda et al [23] postulated that PTSD is depicted by an inhibition of the HPA axis throughout enhanced negative feedback. Yehuda et al [23] hypothesis was originally generated by the discovery of high cortisol suppression in PTSD patients next to low dose of dexamethasone and of a larger dexamethasone-induced decline in cytosolic lymphocyte glucocorticoid receptors in PTSD patients than in those without PTSD. The explanation of high suppression of cortisol in response to dexamethasone dose as prove for enhanced negative feedback rested on the postulation that the dexamethasone suppression test gives a sensitive test of the negative feedback effects of glucocorticoids, especially at the level of the pituitary. The pattern of enhanced negative feedback inhibition at pituitary level is matching with a number of findingrelated to the HPA axis in PTSD patients, including high levels of corticotropin-releasing factor (CRF) in cerebrospinal fluid, diminished ACTH responses to corticotropin-releasing hormone (CRH), and enhanced ACTH responses to metyraponedoses high enough to completely suppress cortisol releaseand cortisol-mediated negative feedback inhibition, especially insofar as these abnormalities occur in the manifestation of depleted or normal cortisol levels [23].

Other study is in disagreement with the viewpoint of enhanced negative feedback inhibition, and explains its data by a greater ACTH response to CRF in PTSD than in comparison subjects [25]This result, accompanied with those of low cortisol levels at

baseline and after dexamethasone administration, hasdeveloped an alternative hypothesis, that PTSD may be characterized by subclinical low adrenal output or adrenal insufficiency[24]. As a consequence, low adrenal output is possibly resulting in a higher ACTH/cortisol ratio, which would be particularly evident if hypothalamic CRF levels were high [23].

The results of present study were found that ACTH/Corisol ratios insignificantly increased in PTSD patients in comparison with healthy group, and this is in agreement with hypothesis of Kanter et al. [24]. Kanter et al. introduced another explanation to the low levels of cortisol when they found high levels of corticosteroid binding globulin in PTSD, which may be partially cause for lower cortisol levels [24].

Although there is accumulating evidence of an association between traumatic stress and the onset of clinical hyperthyroidism, a little of HPT axis studies has been done in PTSD patients [25]. TSH, T_4 and T_3in the present study were insignificantly increased in PTSD patients compared to the control group. Also, there are positive correlations between each of TSH, T_4 and T_3 levels with severity of PTSD symptoms. These findings in concordance with the previous studies in respect to T_4 and T_3 levels, with exceptionof those results of TSH which were found to be decrease in PTSD patients compared to the comparison group, which may be reflect the enhancement of negative feedback of thyroid hormones [8, 25]. Highlevels of thyroid hormone in patients with PTSD, may explain the hyperarousal symptoms of PTSD [8]. The elevation of TSH level in the present study in PTSD patients may affects by low cortisol level which appear to be involved in inhibiting the release of TSH, when such glucocorticoid present in high levels in non-thyroidal illness [26].

In isolation SOD, GPx, and MDA, found to be increased in the present study, whereas, CAT, GSH and albumin were decreased in all groups of PTSD patients, when compared to control group, but this decreases or increases are insignificant. These findings are agreed to those of Tezcan. et al. 2003 [27].

In this study, we try to explain the correlation between oxidative stress and the pathogenesis of PTSD by investigation theassociation of hormonal axes changes with oxidative stress in PTSD patients and control group.

PTSD pathophysiology may also involve dysfunction of the innate immune inflammatory system. PTSD patients have been found to exhibit increased concentrations of circulating inflammatory markers such as C-reactive protein and interleukin-6 (IL-6), suggesting dysfunction of the innate immune inflammatory system. Women with PTSD also shown increased nuclear factor-κB (NF-κB) pathway activity compared to controls and was positively correlated with PTSD severity. These findings suggest that enhanced inflammatory system activity in participants with PTSD is observable at the level of NF-κB, and that in general decreased immune cell glucocorticoid sensitivity may contribute to increased NF-κB pathway activity [28]. Researches on NF-κB from animal models suggest involvement of NF-κB in cerebral ischemia-reperfusion injury, response to neurotrauma, involved in the pathogenesis of human cerebral infarction, and Alzheimer dementia, the atherosclerotic inflammatory disorders associated with the human brain, and in generation of ROS [29].

On the other hand, there are accumulated evidences of an association between traumatic stress and the onset of clinical hyperthyroidism, a few of researches has been focused on hypothalamic-pituitary-thyroid (HPT) axis in PTSD. These studiesand present study have shown an increase in HPT axis activity in PTSD. Especially, the peripheral measurement of both the total and the free of triiodothyronine (T_3) and thyroxine (T_4) have revealed that these are elevated in PTSD patients. In addition, the elevations in T_3 are disproportionately higher than those of T_4, suggesting enhanced peripheral deiodination of T_4 to the more biologically active T_3 form of the hormone (due to differences in its affinity for the binding proteins) with increased aridity for its receptor [30, 31]. This is ensured by the increase of T_3/ T_4 ratio in the present study which reflects increased conversion of T_4 to T_3. This is in agreement with Bunevicius et al study [32]that carried out to evaluateserum TSH, T_4 and T_3 in addition T_3/ T_4ratios reflecting T_4 to T_3 conversion, in women with amenstrually related mood disorder (MRMD). Also, they reported that a history of sexual abuse may identify a clinically distinct subgroup of women with MRMD with respect to HPT-axis function[32].

Previous studies showed that thyroid hormone T_3calorigenesis in the rat involves higher rates of O_2 consumption in the liver, with generation of ROS in hepatocytes and Kupffer cells and antioxidant depletion [33]. This enhancement of status of the oxidative stress of the liver, which is counted a mild redox alteration due to the deficiency of morphologic changes occurrence in parenchymal cell of liver, except Kupffer cells which undergo hyperplasia and hypertrophy [34], was found to trigger the redox regulation of gene expression [33, 35].

Since increased oxidative stress displays a strong correlation with activation of the immune system as well as a number of neuropsychiatric disorders such as PTSD, the antioxidant effects seem to be mediated through direct quenching of ROS by increase the gene expression of major antioxidant enzymes [36].

The insignificant increase in the antioxidant enzymes activities, SOD and GPx, and oxidation product MDA, and the insignificant decrease in the antioxidant enzyme activity CAT, the non-enzymatic antioxidant GSH and albumin, in the present study, may be attributed to thedysregulation of HPA and active HPT axes in PTSD patients.

The insignificant in the outlined results of PTSD patients in the present study may be attributed to long term adaptation with stressful conditions caused by explosion trauma.

Conclusions

The deiodination process of conversion T_4 to T_3 in peripheral tissues is associated with oxygen consumption that generates ROS. Also, the production of H_2O_2 as an essential process for TSH-induced thyroid hormone synthesis is concomitant with generation of ROS. These two processes are altogether produce mild oxidative stress which affects many hormonal axes. This mild oxidative stress increases the NF-κB pathway activity which in turn increases immune cell glucocorticoid sensitivity that leads to decrease cortisol levels.

Figure 1shows schematic diagram that summarizes the postulation of present study of the association between hormonal changes and oxidative stress in PTSD patients.

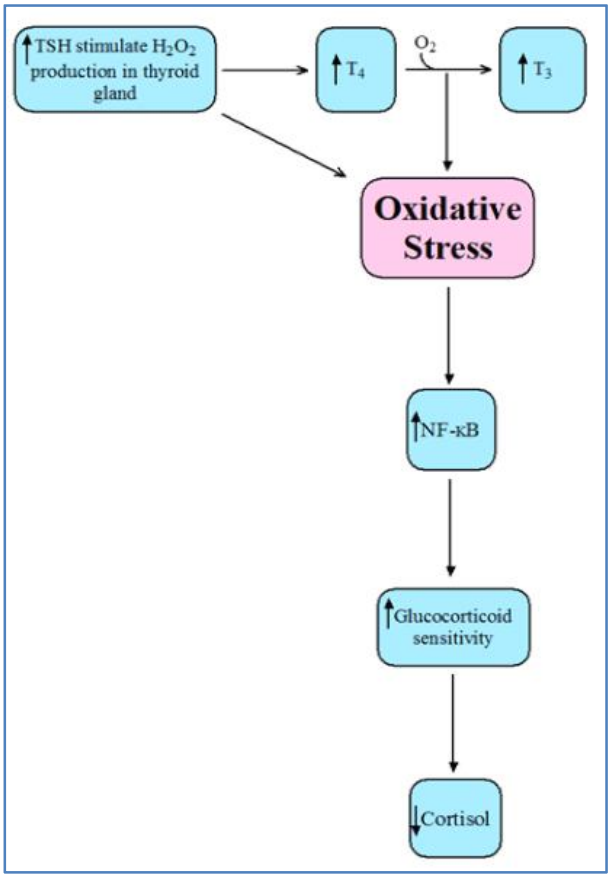

Figure 1 Schematic diagram depicts the association between hormonal changes and oxidative stress in PTSD patients.

Acknowledgment

We would like to thank Mr. Mahmod H. Hadwan, Miss Khowla A. Shemran, Mrs. RanaAbdulali, Mr. Ali Alkufaishi, and Mr. HatamAbdullatif for their wonderful assistance in samples collection and chemicals supplement.

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