International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-3, 2017, pp1658-1666
http://www.bipublication.com

Research Article

Glucocorticoid Receptor Resistance Increment, NMDA Receptor Gene Expression Reduction, and Cognitive Dysfunction after Road Accident Stress

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ABSTRACT
Stress can induce cognitive dysfunction and systemic inflammation. In the present study, attempts were made to show the effects of stress induced by road accidents on cognitive function, systemic inflammation [by means of glucocorticoid receptor resistance (GCR)], and glutamate N-Methyl-D-Aspartate (NMDA) receptor gene expression in 22 patients compared with 22 healthy control volunteers. Blood samples were collected from the participants for cortisol, lymphocyte, neutrophil, and NMDA receptor gene expression evaluation. In addition, participants' cognitive functions were evaluated by using the Paced Auditory Serial Addition Test (PASAT) software. Our data indicated that the neutrophil/lymphocyte ratio and plasma cortisol levels were increased in the stress group (GCR). NMDA receptor gene expression analysis in the peripheral lymphocytes did not detect expression of this gene in the stress group. PASAT data also revealed a comprehensive decrease in the total correct response, mental fatigue, sustained attention, and reaction time in the stress group. In conclusion, it is clear that stress induced by road accident decreases patients' cognitive function, which may be due to an increase in GCR/or decrease in NMDA receptor gene expression.

Key words: Glucocorticoid Receptor Resistance; NMDA Receptor; Paced Auditory Serial Addition Test (PASAT); Road Accident; Stress

INTRODUCTION
Stressful events can induce several consequences, categorized as stress-related disorders, including dementia and other brain dysfunctions, metabolic syndrome, cardiovascular and immune system diseases (Pedersen et al., 2010; Cohen et al., 2012; McEwen, 1998). Experiments have indicated that the hormones and neurotransmitters released during stressful events are among the main mediators for induction of these disorders(Marques et al., 2009). Changes that occur at the cellular and molecular levels, including glucocorticoid hormone release, lead to the production of metabolic disturbances, which in turn cause inflammatory mediators to be release into the bloodstream (Miller et al., 2002). These changes can be modeled via molecular dynamics simulations in order to have a better insight about the mechanism similar to the cell migration mechanism (Shamloo et al., 2014) and HDL (high density lipoprotein) conformation in body(Damirchi et.al, 2016) (Damirchi et al., 2013). Mitochondrial dysfunction may also occur in chronic stress and the glucocorticoid hormones are shown to be involved (Picard et al., 2014). It has been shown that metabolic disturbances after mitochondrial failure may be the basis of mental malfunctions, including dementia, declarative memory reduction, and decision-making weakness (Jeanneteau and Arango-Lievano, 2016).

One of the most important issues after chronic stress is the increase in glucocorticoid receptor resistance or GCR (Cohen et al., 2012; Marques et

al., 2009; Stark et al., 2001), which is the result of a disturbance in immune cell function under chronic plasma glucocorticoid level elevation. Several studies indicated that motor vehicle accidents are among the stressful events that can lead to several mental and physical disorders (Rahmani, 2013; Sadeghi-Bazargani et al., 2016). The possibility that a motor vehicle accident could lead to post traumatic stress disorder (PTSD)(Sadeghi-Bazargani et al., 2016; Undavalli et al., 2014) indicates the importance of studies dealing with cellular and molecular events that occur in the body after a road accident (Undavalli et al., 2014).

In the present study, cognitive function and GCR in the victims of road accidents on Iranian roads were evaluated. In addition, the expression of the N-Methyl-D-Aspartate (NMDA) glutamate receptors in their lymphocytes in peripheral blood was studied.

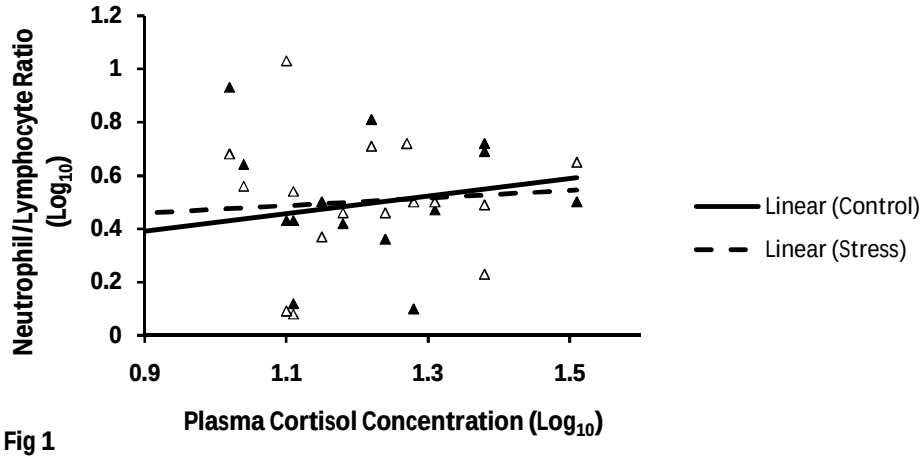

Figure 1: Association between plasma cortisol and neutrophils/lymphocytes ratios for control and stress groups. Lack of correlation is a marker of GCR. Filled triangles/solid line, control group, open triangles/dashed line, stress group (n=17/group).

MATERIALS AND METHODS

Subjects: This research was a cross-sectional study that was carried out on victims of motor vehicle accidents and a control group. The study was conducted for 7 days between November and December, 2014 and included participants who had been in road accidents and a control group who had not experienced motor vehicle accidents. The population under study included 22 participants with road accident histories in the previous 12 weeks who were treated in a hospital in Tehran (Baqiyatallah Hospital). The sampling method was of the continuous type. The participants in the control group were identical to those in the stress group in age, sex, and marital and economic status. The victims which were suffered from head injuries were excluded from the experiments.

Ethical considerations: After obtaining a license from the research committee of Baqiyatallah University of Medical Sciences (27/407/5481–09/16/2014) and coordinating with the hospital manager, we communicated the purpose of the research to the participants and obtained their informed consent to participate in the study. All study protocols were conducted in accordance with the Declaration of Helsinki. The participants were assured that their information remained confidential and that they were free to discontinue their participation at any time.

Measurement tools and method

Personal information, including age, gender, weight, marital status, previous mental disease, and education was collected using demographic questionnaires. To assess plasma cortisol, an ELISA KIT (Cortisol ELISA KIT, Diagnostics Biochem Canada Inc) was used. For this purpose, before subjects began the PASAT (Paced Auditory Serial Addition Test), 10 ml blood samples were collected in 15 mL heparinized

tubes. Five ml of this blood was centrifuged at 3000 rpm for 5 min at 4°C. The supernatant was collected and stored at −20°C until the ELISA measurements was performed.

Calculation of GCR

GCR calculation was performed as described earlier (Cohen et al., 2012). Briefly, cortisol evaluations wasperformed and then percentages of neutrophils and lymphocytes were obtained and the neutrophil to lymphocyte ratio (N/L%) calculated. The GCR was then calculated by plotting Log_{10} of this ratio against Log_{10} of cortisol concentration. A lack of correlation was considered as a marker of GCR (Cohen et al., 2012).

NMDA receptor gene expression

The remaining five ml of blood sample was centrifuged in ficol medium for lymphocyte separation. The lymphocytes then were processed for RNA extraction, and Real-Time-PCR was performed for NMDA receptor gene expression.

PASAT performance

To assess functional cognitive improvement, the PASAT software was used. The PASAT is performed by presenting 60 pairs of single-digit numbers and asking the subject to add the last two numbers. For example, if the numbers 3, 4, 2, 6, and 1 are presented, the subject should answer with the numbers 7, 6, 8, and 7. It has been demonstrated in reports that the PASAT software test is such a difficult test that the individual may not even be willing to continue. In a previous study, the PASAT software was used to examine the effects of aromatherapy on general mental health (the total number of correct responses), sustained attention (the longest sequence of consecutive correct responses), reaction time (average reaction time), and mental fatigue (the longest sequence of consecutive incorrect responses). The reliability and validity of the PASAT software have also been confirmed in different studies and societies in Iran (Erfani et al., 2016; Pourhashemi et al., 2016).

Statistical analysis

Data are shown as mean ± SEM of the % change in variables for PASAT software factors. These data were statistically analyzed using an unpaired *t*-test. Demographic data were analyzed using chi-square analysis. The GCR was calculated on the basis of the associations of plasma cortisol concentration [log_{10}] with the ratio of neutrophils to lymphocytes (N/L%) [Log_{10}]. The statistical calculations were performed using SPSS software version 20. P <0.05 was considered to indicate a significant difference.

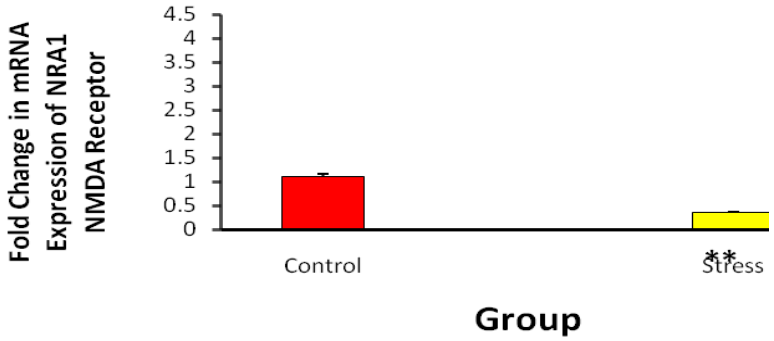

Fig 2

Figure 2: Change in the NMDA receptor gene expression in the stress and control groups. Our data showed that the expression of NMDA receptor gene in the stress group is reduced in comparison with control group. **P<0.01 different from control group (n=6/group).

RESULTS

Demographic analysis of the participants

All of the participants completed the test. None of the participants were married. The mean age of the participants in stress group was 21.7 ± 0.35 years, their weight was 68.4 ± 1.1 kg, and their height was 173.5 ± 3.7 cm. These parameters were 22.43± 0.57 years, 67.3±1.3 kg, and 169.83 cm for

control group, respectively.

GCR assessment in the stress and control groups

The results of our experiment showed that in the stress group, there was no correlation between plasma cortisol concentration and N/L%, which indicated the GCR. However, there was a clear correlation between these two variables in the control group, indicating the absence of GCR (Fig 1).

NMDA receptor gene expression

The data obtained in our experiment are showed in figure 2. As it is clear in the figure, the NMDA receptor gene expression in the stress group was reduced as compared with the control group (t_5=2.13, P<0.01).

PASAT software data analysis

The results demonstrated that cognitive variables, including general mental health, sustained attention, and reaction time were significantly reduced in the stress group as compared with the control (Fig 3A-C). However, mental fatigue in the stress group was significantly increased (Fig 3D). General mental health (t_{43} = 2.8, P < 0.01), reaction time (t_{43} = 2.78, P < 0.05), sustained attention (t_{43} = 3.29, P < 0.01), mental fatigue (t_{43} = 3.21, P < 0.01).

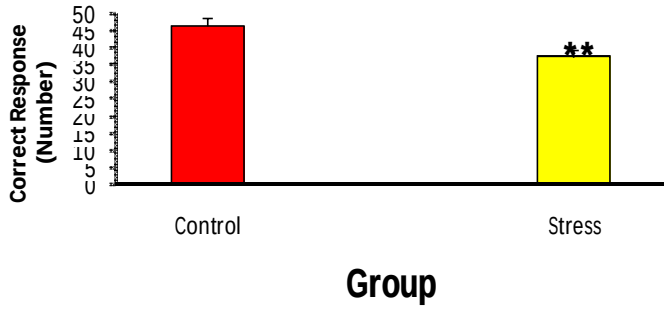

Fig 3A

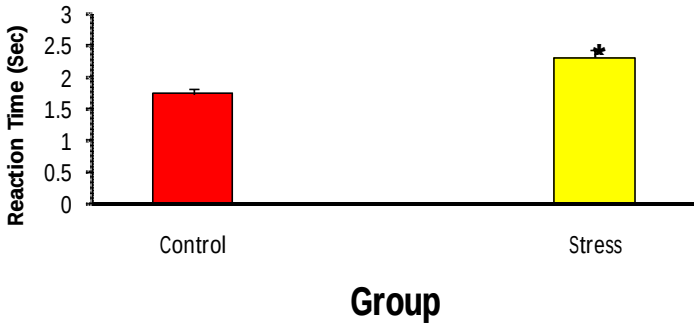

Fig 3B

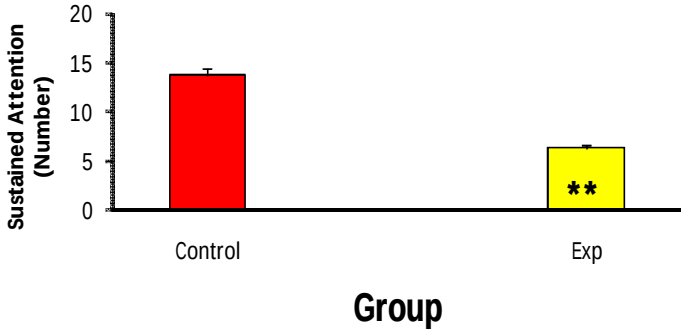

Fig 3C

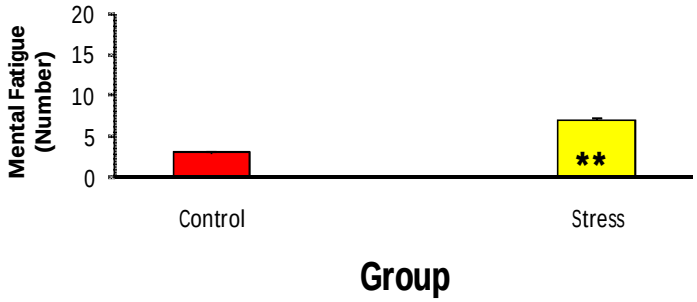

Fig 3D

Figure 3: Changes in the General Mental Health (3A), Reaction Time (3B), Sustained Attention (3C), and Mental Fatigue (3D) in the participants before and after the intervention. As it is shown in the figure, all the factors were improved after 90 days saffron extract consumption. *P<0.05, and **P < 0.01 difference between the before and after tests (n=22/group).

DISCUSSION

In this study the effects of stress caused by road accidents on brain cognitive functions, hormonal (cortisol) changes, immune system activity, and expression of the NMDA receptor gene in the victims was evaluated. Previous research has shown that stress resulting from road accidents can be classified in the category of severe stress and may even lead to PTSD(Sadeghi-Bazargani et al., 2016; Undavalli et al., 2014). Previous research also emphasized that stressed people and people who are receiving glucocorticoids may show signs of damage to their verbal memory(Lupien et al, 2002), spatial memory(Lupien and Schramek, 2006), and/or decision making after the accident(Wolkowitz et al., 1997). These findings may indicate the damaging effect of glucocorticoids secreted by the adrenal glands during stress on the memory and decision making areas of the brain, especially the hippocampus and prefrontal cortex(McEwen et al., 2016). In our research, stressed participants also sustained a dramatic reduction in their short-term memory compared with the control group. A reduction in decision-making abilities, increased mental fatigue, and reduced sustained attention in the stressed group also indicated the intense effect of road accident stress on brain cognitive functions. Previous research has shown that stressed people usually cannot make right decisions and typically have trouble in both simple and complex calculations(Bizik et al., 2013; McEwen, 2016). Animal model studies indicate that the glucocorticoids released during stress activate their receptors (type 1 and especially type 2 glucocorticoid receptors) located in the cytoplasm of cells in CA1, CA3, and dentate gyrus regions of the hippocampus and induce rearrangements of these cells' communications and eventually reduce their performance(Vyas et al., 2002). These rearrangements include cytoskeleton protein reduction and thus reduction in the volume and size of cells, reduction in neurotransmitters turn over, reduction in the number of dendritic spines, reduction in the size and number of neuronal dendritic arborization(Duman et al., 2016), and most importantly, reduction in the ATP production ability in these neurons which in turn reduces their metabolic function(Du et al., 2009). All of the above mentioned facts may lead to a reduction in the memory and decision making ability in stressed subjects(McEwen, 2012).

On the other hand, general mental health in stressed individuals in our study decreased. Previous studies have shown that subjects, that have suffered an injury in the cerebral cortex, score lower in the PASAT software test, which indicates that they have deteriorated general mental health(Sherman et al., 1997). Investigators insist that worse general mental health reflects the impact of the brain injury on cognitive functions(Deary et al., 1991). However, subjects tested in the present study did not have a skull

injury; hence, we concluded that the lower general mental health score in stressed subjects was indicative of the impact of the stress experience on them. In this regard, previous studies have shown that subjects with different stress experiences had lower general mental health scores(Erfani et al., 2016; Pourhashemi et al., 2016). This study did not show a significant difference between the two groups in anthropometric indices. Several studies showed that anthropometric indices in people who have chronic stress are higher than in healthy people(Wiley et al., 2016). For example, one study has shown that poor sleep and sleep deprivation as an allostatic load, increases body weight and BMI(Zimmermann, 2016; Zimmermann, 2011). On the other hand, these subjects suffered from metabolic syndrome as compared with normal healthy subjects(Komulainen et al., 2006). Research has also shown that subjects who suffered from metabolic syndrome usually suffered from chronic stress and showed lower cognitive functions(Zimmermann, 2016; Komulainen et al., 2006). The lack of difference between healthy and stressed groups in our study may be due to the shorter time from the onset of stress in the stressed group (less than 100 days). This time may have been insufficient for the induction of metabolic syndrome. Our data showed that plasma cortisol in the stressed group was dramatically higher than in the control group. Since cortisol is considered to be the main hormone released in response to stress(Yehuda et al., 1995), it seems that the plasma cortisol increment in the stressed group indicated an HPA axis hyper activity in this group. In fact, because of a lack of participants' cooperation we did not perform dexamethasone challenge tests, and did not measure plasma cortisol for 24 h and this is the main weakness of the present study. However, regarding the existence of a severe stressful events one can conclude that higher plasma cortisol in the stressed group may be a hazardous factor for these subjects. In agreement with our finding, studies on human (Morgan Iii et al., 2001)and animal models (Tort et al., 1996)also indicated that the HPA axis is activated during stress and plasma glucocorticoid levels increase. In addition, plasma glucocorticoid returns to lower levels when the stress becomes chronic(Miller et al., 2007). However, our study was performed 90 days after trauma and it is an important finding that the severity of stress may increase the HPA axis sensitivity so that after this time, its activity still remains higher. What consequences can this high cortisol level produce? Several data indicated that chronic plasma glucocorticoid level elevation is associated with weaker functioning of the immune system(Segerstrom and Miller, 2004). Studies indicated that a malfunction of the immune system can be investigated using the GCR of the subjects(Cohen et al., 2012; Marques et al., 2009; Stark et al., 2001; Gotovac et al., 2003). Our data indicated that the GCR in the stressed group was significantly higher than in the control group. Other studies have also shown that stressed individuals have a higher GCR and are under greater risk of suffering from an infectious disease(Marques et al., 2009; Stark et al., 2001). The importance of our finding is that stressed subjects may become with GCR and according to previous studies, they may be at risk of infectious and/or other stress-related diseases.In the last part of our experiments, the expression of the NR1 subunit of the glutamate NMDA receptor genes in the peripheral blood lymphocytes was lower than in the control group. Studies indicated that NMDA receptors are involved in cognitive functions including memory processes in the brain(Moghaddam et al., 1997; Malhotra et al., 1996). In addition, their expression in the peripheral blood lymphocytes is in direct relation to the expression of these receptors in the brain(Miglio et al., 2005). Considering these facts, it is interesting that the expression of these receptors was reduced in stressed subjects. This finding was associated with the PASAT software section which indicated a cognitive function reduction in stressed subjects.

CONCLUSION

In conclusion, our study indicates that severe stress events such as car accidents can produce several hazardous side effects including cognitive

function reductions, GCR, and reductions in the NR1 NMDA glutamate receptor subunit which can interfere with normal life functions in these subjects. Although we did not investigate the function of the gastrointestinal system in this study, partly because of the short time elapsed between the stress accident and the study, we recommend this function as well as the cardiovascular system function must be considered in future studies in broader time scale research.

ACKNOWLEDGMENT:

The authors would like to express their thankfulness to the participants in the study for their corporation.

DECLARATIONS

Authors' contributions

HS design the experiments, involved in drafting the manuscript and performed the analysis and interpretation of data; HG performed the experiments and help the analysis of data; HA involved in drafting the manuscript.

Competing interests: The authors declare that they have no competing interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, ornot-for-profit sectors.

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