

Original Article

Effects of Stress on Serum and Hippocampal IL-1 β and Glucose Levels as well as Retention in Rats

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Abstract

Objectives: Stress is defined as a potential risk factor in the development of different neuropsychological disorders. Chronic stress dramatically affects retention as memory. The present study investigated the effects of different stress durations and recovery periods on serum and hippocampal IL-1 β and glucose levels as well as retention in rats.

Methods: Rats were randomly allocated to four groups: Control -(Co), Stress-Rest -(St-Re), Rest-Stress -(Re-St), and Stress-Stress- (St-St). Restraint stress was applied 6 h/day over the two experimental periods of 21 and 42 -days.

Results: The total dark compartment stay time- (DS) in the passive avoidance test was used for the assessment of retention at different intervals. Findings indicated that retention was significantly impaired at different intervals in the Re-St and St-St treatment groups compared to the Co; however, no indication was found that these changes occurred via enhanced IL-1 β and glucose levels.

Conclusion: There may have been protective mechanisms involved hindering the changes in IL-1 β and glucose levels in the hippocampus. Also, much longer stress durations might lead to adaptive effects on the variables.

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Introduction

Stress is defined as any endogenous or exogenous change in the environment that disturbs the maintenance of the brain homeostasis (1, 2) and that triggers physiological and behavioral responses

in the body and brain (3). It can introduce a bias towards stress-related diseases via such different contributors as adrenal glucocorticoids (4), brain derived neurotrophic factor (BDNF), and interleukin-1 beta (IL-1 β) (5-7). The nervous system produces and releases inflammatory factors (e.g., cytokines) activated in response to different stressful stimuli (8). Some study have shown that cytokines are involved in cognitive functions (9, 10) and play an important role not only in the functioning of the brain but in the modulation of neuroendocrine, neural, and behavioral functions as well (11). On the other hand, IL-1 β receptors are considered to be localized in the rodent brain with particularly high densities in the hippocampus (12). Moreover, IL-1 β causes endocrine variations often associated with stress and anxiety (13). It has been suggested that IL-1 β has stress-like effects on the activity and behavior of both the neurotransmitters and the hypothalamic-pituitary-adrenal axis (HPA) (13). Evidence, however, indicates that significant alterations occur in the glucose level in response to stress (14). Also, administration of glucose has been found to enhance memory regarding many behavioral tasks in animals (15). In previous studies, the present authors investigated the interactions among learning, memory, latency of the passive avoidance test, plasticity, long-term potentiation, and certain mediators in stressed rats (16, 17). In line with those studies, it is the objective of the present investigation to evaluate the effects of chronic stress and post-stress recovery period on retention and other pathophysiological mechanisms such as serum and hippocampal IL-1 β and glucose levels in rats. A second objective is to show the interaction among these variables in stressed subjects.

Materials and Methods

Experimental animals

Experiments were performed on 40 male Wistar rats with an initial weight of 250–300 g obtained from the Jondishapour Institute, Ahvaz, Iran. All the experimental protocols were approved by the Ethical Committee of Isfahan University of Medical Sciences (Isfahan, Iran) in compliance with the “Principles of Laboratory Animal Care” and “the European

Communities Council Directive of 24th November, 1986 (86/609/EEC)”. Rats were housed in a light-controlled (12-h light/dark; lights on 07:00–19:00) room with a temperature of 22 \pm 2°C. Food and water was made available *ad libitum*, except during the stress treatment periods. All the behavioral experiments were carried out from 14:00 to 15:00. The animals in all the treatment groups were subjected to the passive avoidance learning test on day 21. The experiments lasted for 42 days.

The rats were randomly assigned to four groups (n =10 in each) as follows: 1) Control (Co), in which rats received no special treatment but were only transferred to the laboratory and handled in a manner similar to that employed for the experimental animals throughout the study period; 2) Stress-Rest (St-Re, stress with recovery) group, in which restraint stress was applied 6 h/day for 21 days before the rats were relieved at rest for 21 days; 3) Rest-Stress (Re-St, stress without recovery) group, in which the rats received no special treatment for 21 days but only then subjected to chronic restraint stress 6h/day for 21 days; and 4) Stress-Stress (St-St; sustained stress) group, in which the rats were maintained under restraint stress 6 h/day for 42 days.

Experimental procedures

Stress paradigms

For the purposes of this study, the rats were placed in Plexiglas cylindrical restrainers and fitted tightly there for 6 h/day (8:00–14:00) for 21 days or for 42 days in the chronic stress model (16-19). This kind of stress was a strong stressor for rats (20).

Behavioral apparatus and method

The passive avoidance apparatus was divided into two compartments (light and dark) separated by a sliding guillotine door. The test itself consisted of three phases: habituation (no electrical foot shock used), acquisition trial (electrical foot shocks used), and retention test (no electrical foot shock given). On day 20 of the experiment, each rat was habituated to the apparatus for 300 Sec. On the following day, an acquisition trial was performed in which the rats were individually placed in the light compartment for

60 Sec after which the guillotine door was raised. Once a rat entered the dark compartment, the door was closed and an inescapable scrambled single foot electric shock (50 Hz, 0.2 mA, 3s) was delivered through the grid floor by an isolated stimulator. Each rat had three retention trials on days 1, 7, and 21 after a training trial. During the probe trials, the rats were placed in the light compartment again with access to the dark compartment without any shock. The total time spent in the dark compartment was recorded. The passive avoidance task determined the ability of the animal to remember the foot shock received. Avoiding entry into the dark compartment or a longer duration of stay in the light compartment was interpreted as a positive response.

Assessment of serum and hippocampal IL-1 β and glucose levels

At the end of the experimental period, the animals were anesthetized with urethane (1.5 g/kg, i.p.) and sacrificed at 14:00-15:00 by decapitation on day 43. In each case, the brain was immediately removed from the skull and the hippocampus was instantly dissected and kept on dry ice. Each hippocampus was immersed in ProblockTm-50, EDTA free (Gold Bio Co.; USA) and a phosphate buffer solution (PBS buffer, 0.01 M, pH 7.4). The solution contained a complete protease inhibitor cocktail. Then, the hippocampi were homogenized and centrifuged in a cooled centrifuge (4°C, 10,000 g for 20 min). The supernatant was collected and stored at 80°C until assessment. In addition, blood samples were obtained from the trunk blood; the serum was separated and stored at 80°C until analysis. The IL-1 β and glucose levels in the hippocampal homogenate were measured using the IL-1 β ELISA kit (Koma biotech Inc., Gangseo-gu Seoul, Korea) according to the glucose oxidase method (Parsazmun Co., Tehran, Iran).

Measurement of body, brain, and hippocampus weights

At the end of the experimental period, hippocampus, brain, and final body weights were measured for each rat and the correlation among them was determined.

Data analysis

Total stay time in the dark compartment of the

passive avoidance test was analyzed using the Kruskal-Wallis non-parametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann-Whitney U test.

Other data were analyzed by ANOVA followed by the Tukey's post-hoc test for multiple groups. In addition, Pearson's correlation analysis was performed to find the correlations among the variables. The values thus obtained were reported as Means \pm SEM, where $P < 0.05$ is considered statistically significant. Ultimately, the calculations were performed using SPSS 21 software (SPSS Inc., Chicago, Illinois, USA).

Results

Total dark compartment stay time

The statistical analysis of the total time spent in the dark compartment (dark stay; DS) revealed that the stressed groups had significant enhancements ($P < 0.05$; in all of them) on day 1 after the foot shock compared to the control (Co) group (Fig. 1). The analysis also indicated that exposure to the stressor had interfered with the retention deficit.

As shown in Fig. 1, the day-7 DS values of the stress with recovery (St-Re), stress without recovery (Re-St), and continual stress (St-St) groups were significantly higher ($P < 0.05$, $P < 0.001$, $P < 0.001$, respectively) than that of the Co group. Furthermore, in the Re-St and St-St groups, the DSs on day 7 were significantly higher ($P < 0.01$, for both) than that of the St-Re group.

The day-21 DS of the St-Re group was not significantly different from that of the Co group (Fig. 1). As shown in Fig. 1, the day-21 DSs recorded for the Re-St and St-St groups were significantly higher than that of the Co group ($P < 0.001$, for both). However, the day-21 DSs were remarkably higher after the electrical foot shock delivery in the Re-St and St-St groups ($P < 0.01$) than that observed in the St-Re group.

The total DS times were analyzed over three trials using the relevant sample so as to evaluate the

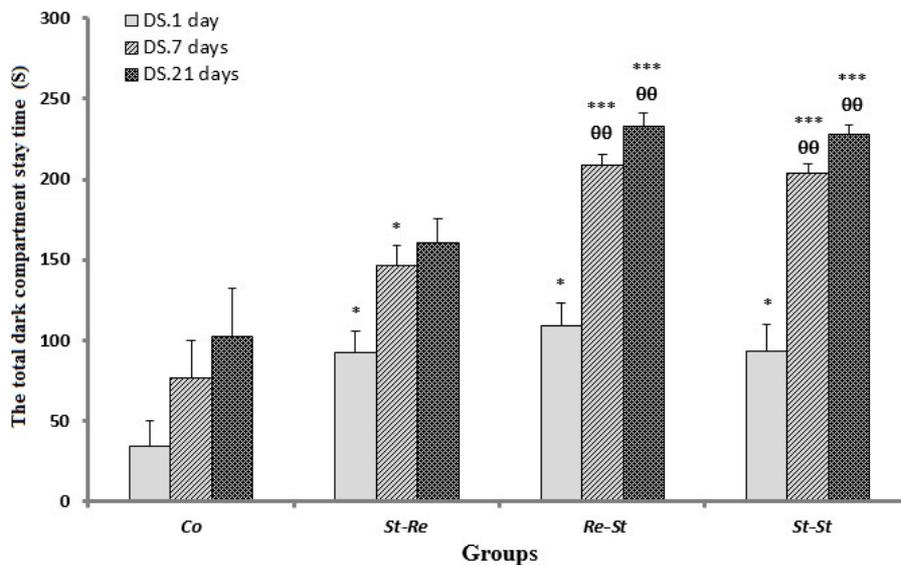


Fig. 1: Total dark compartment stay time (DS) of the passive avoidance apparatus during retention test 1, 7, and 21 days after electrical foot shock delivery in the different treatment groups (between groups, n=10). Results are expressed as means±SEM (Kruskal -Wallis test, Mann-Whitney U test; *P<0.05, ***P<0.001 when compared to the Co group; ⁰⁰P<0.01 when compared to the St-Re group in each trial).

Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

differences within each group. Thus, the values obtained on days 1 and 7, 7 and 21, and 1 and 21 were compared for each group (Fig. 2).

In the Co group, no significant differences were detected among the DSs of day 1 vs. day 7, day 7

vs. day 21, and day 1 vs. day 21 after the electrical foot shock delivery. Nevertheless, the St-Re, Re-St, and St-St groups exhibited significant differences (P<0.01) with similar comparisons (Fig. 2). In general, DS time increased in all the groups as days went by.

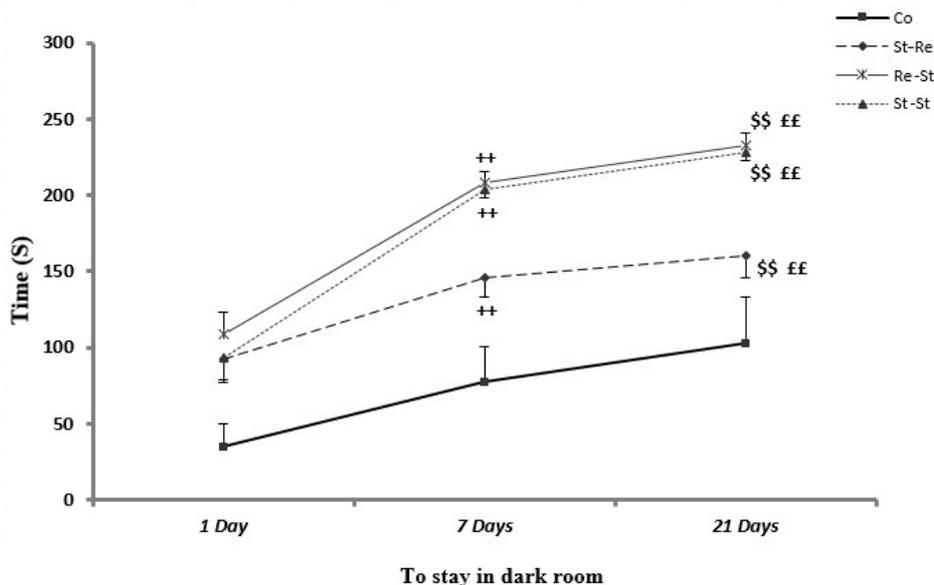


Fig. 2: Trend line of the total dark compartment stay time after electrical foot shock delivery (within groups). Results are expressed as means±SEM (Friedman test, Wilcoxon signed ranks test; **P<0.01, ^{SS}P<0.01 and ^{EE}P<0.01 for the DS values in day 1 vs. day 7, day 7 vs. day 21 and day 1 vs. day 21, respectively).

Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

Assessment of serum and hippocampal IL-1 β and glucose levels

Based on the ANOVA and post-hoc Tukey's results, a significant increase ($P < 0.01$) was observed in the serum IL-1 β of the Re-St group compared to that of the Co group. Also, in the Re-St group, the serum IL-1 β level was significantly higher ($P < 0.05$) than that in the St-Re group (Fig. 3). Hippocampal IL-1 β levels of all the groups were not significantly different from each other, suggesting that the brain probably had protective mechanisms against the changes in IL-1 β

levels and/or that more IL-1 β had been produced in the peripheral organs than in the hippocampus (Fig. 3).

Serum glucose levels in the Re-St and St-St groups significant ($P < 0.01$ and $P < 0.05$, respectively) also exhibited differences with those of the Co group. Additionally, a significant ($P < 0.05$) enhancement was observed in the glucose levels of the Re-St rats compared to the St-Re group. No significant increase was, however, observed in this parameter in the St-St group (Fig. 4).

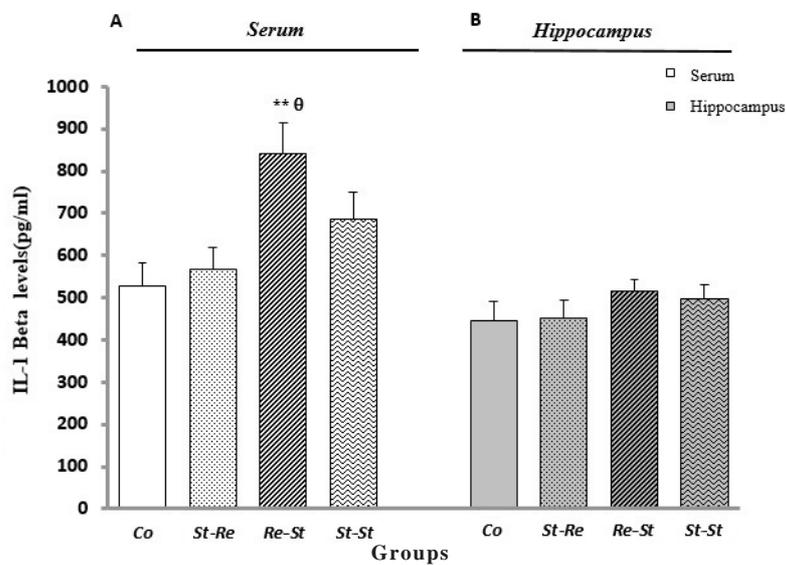


Fig. 3 : Effects of chronic restraint stress on serum and hippocampal IL-1b levels in the different treatment groups (n=10). Results are expressed as means \pm SEM (ANOVA test, Tukey's post- hoc test; ** $P < 0.01$ when compared to the Co group; $\theta P < 0.05$ when compared to the St-Re group). Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

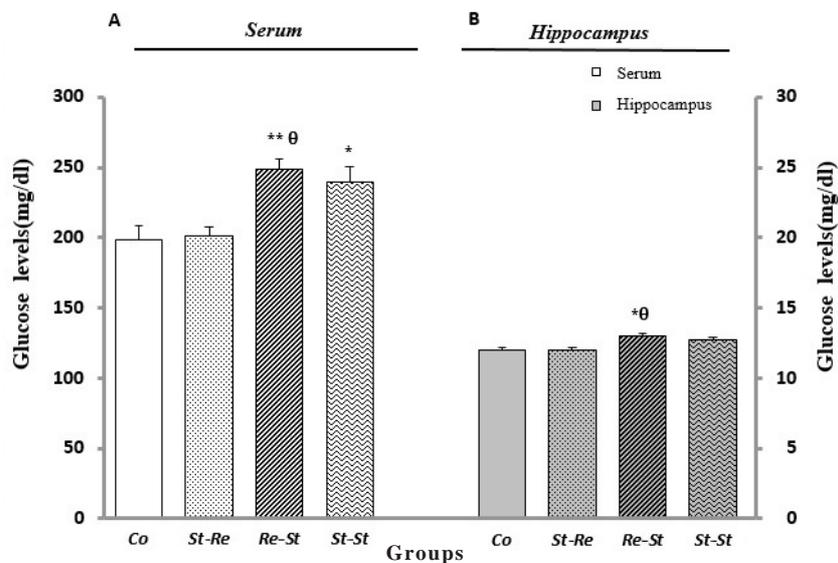


Fig. 4 : Effects of chronic restraint stress on the serum and hippocampal glucose levels in the different treatment groups (n=10). Results are expressed as means \pm SEM (ANOVA test, Tukey's post-hoc test; * $P < 0.05$, ** $P < 0.01$ when compared to the Co group; $\theta P < 0.05$ when compared to the St-Re group). Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress-Stress group.

In the Re-St group, hippocampal glucose levels were significantly ($P<0.05$) different from those of both the Co and the St-Re groups. Accordingly, a 21-day recovery period after the chronic stress may be effective for the improvement of both serum and hippocampal glucose levels (Fig. 4).

Correlation between serum and hippocampal IL-1 β levels

Our analysis revealed a significantly positive correlation between the serum and hippocampal IL-1 β levels in each experimental group. However, these correlations were observed in the Co (Pearson's correlation; $r=0.859$, $P<0.01$), St-Re ($r=0.820$, $P<0.01$), Re-St ($r=0.883$, $P<0.01$) and St-St ($r=0.861$, $P<0.01$) groups (Fig. 5), indicating the probability that IL-1 β was able to cross the blood brain barrier (BBB).

Correlation between serum and hippocampal glucose levels

Present findings indicate a significantly positive correlation between the serum and hippocampal glucose levels in each experimental group. These correlations were observed in the Co (Pearson's correlation; $r=0.738$, $P<0.05$), St-Re ($r=0.685$,

$P<0.05$), Re-St ($r=0.777$, $P<0.01$) and St-St ($r=0.765$, $P<0.01$) groups (Fig. 6). These findings also confirm the above conclusion that IL-1 β probably crosses the blood brain barrier (BBB).

Final body, brain, and hippocampus weights

The weights of hippocampus and brain were not significantly different in each experimental group. Meanwhile, compared to the Co group, only the final body weight of the Re-St group indicated a significant reduction ($P<0.05$) (Fig. 7). It seems that food intake had changed in the animals under stress conditions.

Correlation among final body, brain, and hippocampus weights

No significant correlation was found between the final body and brain weights in any of the groups (no graph provided).

Present findings, however, showed a significantly positive correlation between the brain and hippocampus weights across the experimental groups. These correlations were observed in the Co (Pearson's correlation; $r=0.699$, $P<0.05$), St-Re ($r=0.668$, $P<0.05$), Re-St ($r=0.830$, $P<0.01$), and St-St ($r=0.690$, $P<0.05$) groups (Fig. 8). These findings

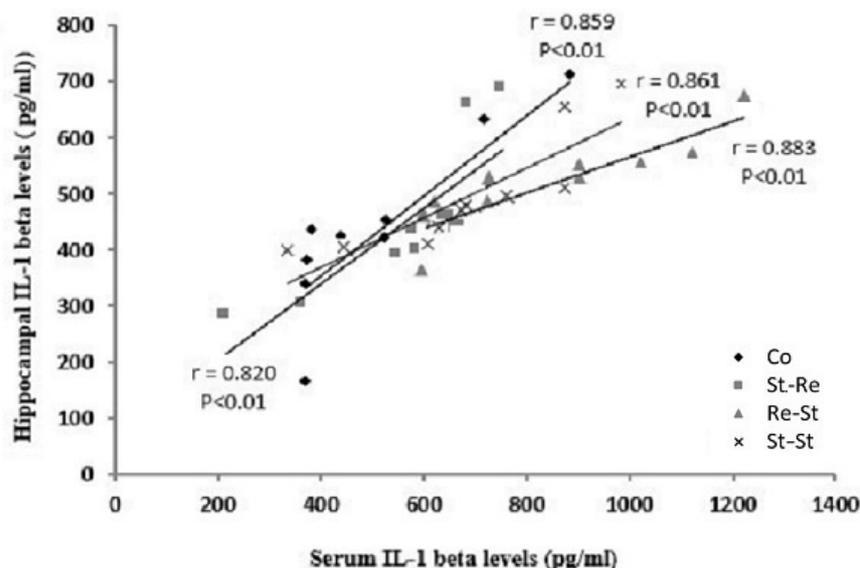


Fig. 5: Correlation analysis of the serum and hippocampal IL-1 β levels in the different treatment groups ($n=10$). Results are expressed as means \pm SEM (Pearson's correlation test).

Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

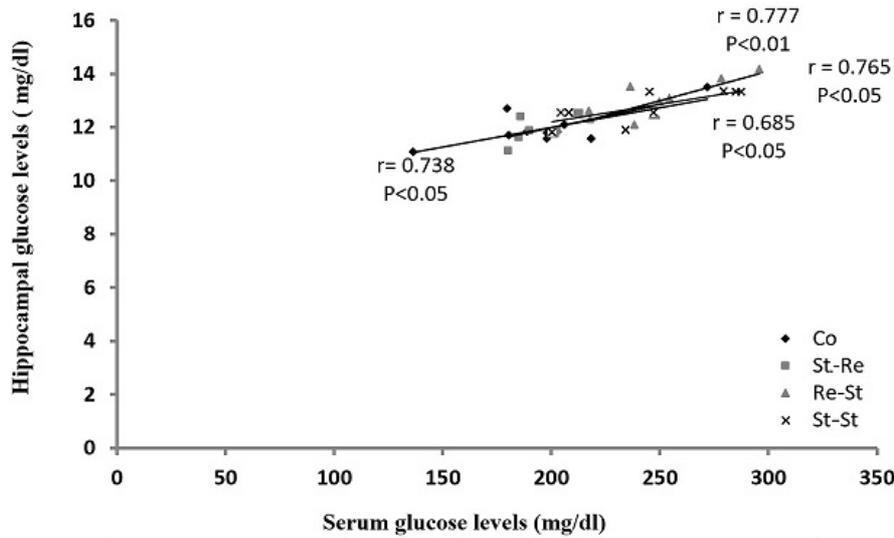


Fig. 6 : Correlation analysis of serum and hippocampal glucose levels in the different treatment groups (n=10). Results are expressed as means±SEM (Pearson’s correlation test).
Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

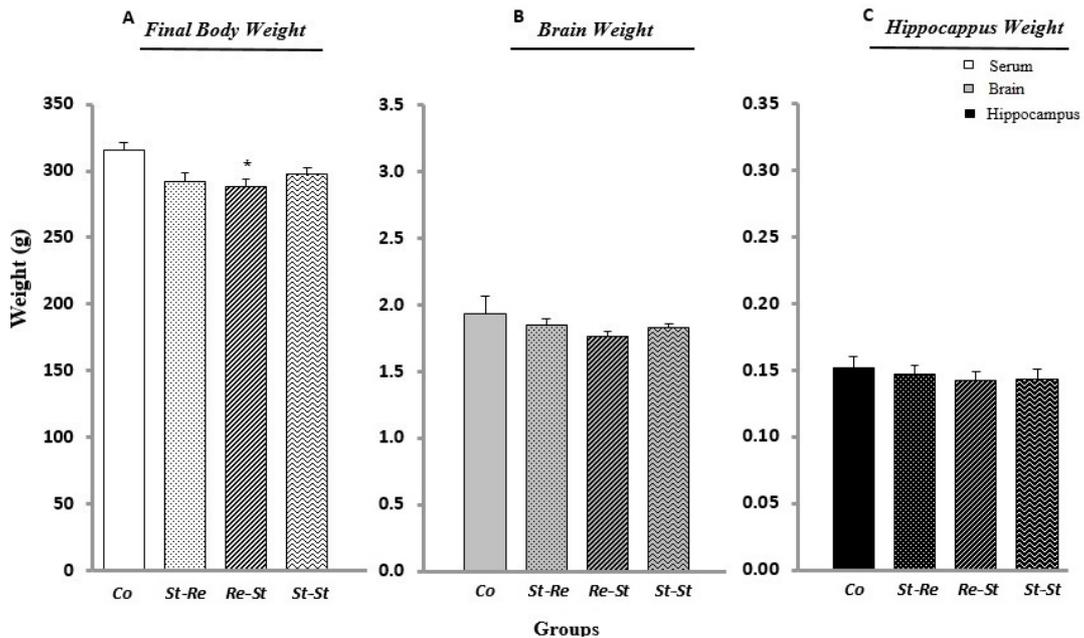


Fig. 7 : Comparison of hippocampus, brain, and final body weights in all the treatment groups (n=10). Results are expressed as means±SEM (ANOVA test, Tukey’s post-hoc test; *P<0.05 when compared to the Co group).
Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

indicate permanent positive correlations between the hippocampus and the brain in all the experimental groups.

Discussion

It may be concluded from the increased stay time in the dark compartment (DS) in the stressed groups

that chronic stress causes retention impairments in all such groups (Figs. 1 and 2), a finding in line with previous studies (4, 16, 17, 20). Stress may, therefore, accelerate the onset of numerous neuropsychological disorders (21).

Based on our findings, chronic stress followed by a recovery period (St-Re group) notably enhanced the

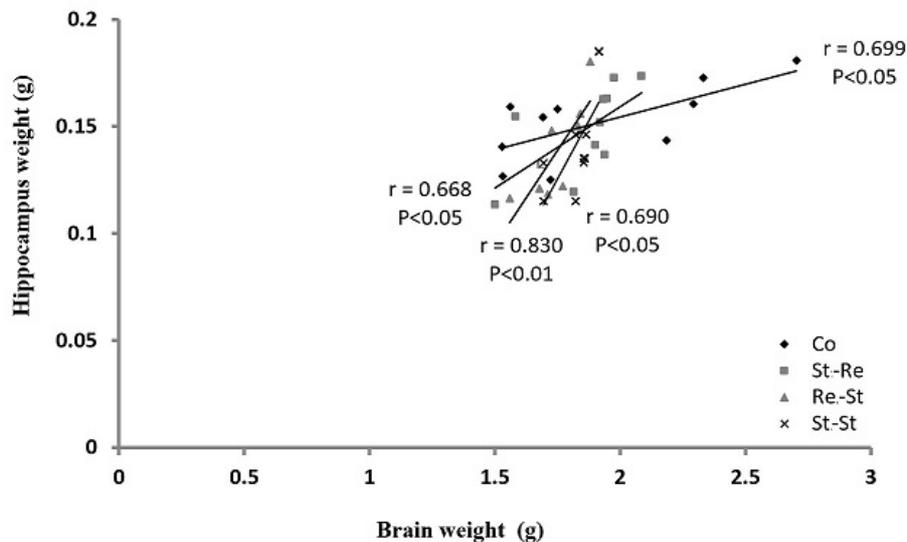


Fig. 8 : Correlation analysis of the hippocampus and brain weights in the different treatment groups (n=10). Results are expressed as means±SEM (Pearson's correlation test).

Co: Control group; St-Re: Stress-Rest; Re-St: Rest-Stress group; St-St: Stress -Stress group.

DS time on days 1 and 7 (Figs. 1 and 2). No adaptations were observed in the retention of the passive avoidance test on days 1 and 7 after inducing the chronic stress, a finding that is confirmed by previous studies (22, 23). IL-1 β and glucose levels were observed in the current study to return to their basal levels during the recovery period following the chronic stress. It may, therefore, be claimed that long-term recovery periods (e.g., 21 days) should be able to eliminate the effects of chronic stress on retention as well as the serum and hippocampal IL-1 β and glucose levels. This is while studies suggested that a 21-day recovery period after stress was not enough for producing changes in behavior or in biochemical factors (24).

On the other hand, chronic stress without a recovery period (Re-St) was found to impair day-1 retention, particularly those of days 7 and 21 (Fig. 1). Other studies have demonstrated that stress is an important factor potentially altering the brain cell morphology and disturbing retention (25), especially the spatial memory in rodents (26). In contrast, one report indicated that animals were able to habituate to chronic stress (27). The present data reveal that chronic stress significantly increases IL-1 β levels in the serum, but not in the hippocampus, suggesting that brain probably had protective mechanisms against any change in its IL-1 β levels (Fig. 3). A

number of protective endogenous mechanisms may be involved in regulating and reducing IL-1 β levels and its activities in the hippocampus; these include enhancement of the levels of acetyl cholinesterase (AChE) inhibitors that inhibit the production of the IL-1 β from macrophages and microglia (28-30), enhancement of the production and secretion of IL-1 β receptor antagonist (IL-1ra) and other anti-inflammatory cytokines and hormones, and changes in the number of IL-1 receptors (31). Study has shown that IL-1 β responds to the stress in the brain (32). It has also been shown that excess levels of IL-1 β impair the retention processes and neural plasticity (11). Our previous study showed that enhancement of hippocampal corticosterone levels and decrement of the brain-derived neurotrophic factor (BDNF) were involved in memory impairment caused by chronic stress (16). Certain reports have indicated that enhanced plasma cytokines and elevated HPA axis activity induced changes in the BDNF and memory (5, 33). While our present findings revealed no significant changes in the hippocampal IL-1 β , the results of our previous study (16) showed significant differences in the hippocampal BDNF and corticosterone levels. Hence, the hypothesis that emerges from both our previous (16) and present results is that BDNF levels were not probably affected by the IL-1 β levels in the hippocampus but that corticosterone level was probably a more effective

factor in the changes observed in IL-1 β levels. Such inconsistencies in the results can be possibly accounted for by a variety of parameters such as the behavioral tests conducted or the duration and intensity of the stress induced (34, 35).

Current data also indicated that chronic stress significantly increased glucose levels in the serum and hippocampus (Fig. 4). Nevertheless, longer stress duration had modulating effects on the serum and hippocampal glucose levels. One study reported that plasma glucose levels increased after IL-1 β administration (36). Meanwhile, *in vivo* study has shown that IL-1 β induces hypoglycemia in rats and mice (37). It may be inferred from our previous (16) and present findings that glucose levels in serum and hippocampus are functions of corticosterone (CORT) changes more than they are of IL-1 β changes under stress. Moreover, some reports have demonstrated that IL-1 β stimulates the HPA axis and affects glucose homeostasis (38, 39). The interaction among these factors might have implications for brain plasticity and the behavioral changes induced following stress-involved experiments (16, 40). Thus, multiple factors seem to be involved, via many different mechanisms, in the retention deficit under stress (41). Accordingly, it may be concluded that, under stress, the immune and neuroendocrine systems affect retention in similar manners.

The retention impairments observed in the present study were slightly modulated in the continual stress (St-St) group when compared to the Re-St group (Fig. 1-2). Compared to the 21-day chronic stress, very long stress durations (42 days), therefore, showed partially adaptive mechanisms in rats. One study, however, reported that chronic stress accelerated the onset and severity of cognitive disorders (21). Moreover, we found no major differences in the IL-1 β and glucose levels between the Rest-Stress and Stress-Stress groups; thus, adaptation happened after 21 days in stressful conditions. Our previous electrophysiological study of hippocampus yield similar results. Thus, an elapse of 42 days led to no significantly greater improvements in the responsiveness, paired-pulse response, or long-term potentiation than what is achieved after 21 days. However, the small

insignificant changes observed were indicative of adaptation (17). Reportedly, certain physiological and behavioral consequences have been observed to eliminate in animals repeatedly exposed to the same stressor (42), suggesting adaptation of the animals to the stress conditions over extended periods. Thus, both physiological and behavioral changes might play critical roles in maintaining retention.

Another finding of the present study was the higher concentrations of IL-1 β and glucose in blood serum than in the hippocampus. In addition, the serum and hippocampal IL-1 β and glucose levels were directly and significantly correlated within the individual groups (Figs. 5 and 6). It seems that, although serum IL-1 β and glucose are capable of crossing the blood brain barrier (BBB), this barrier limits the access of IL-1 β , and particularly glucose, in the hippocampus. It might be hypothesized that corticosterone prevented glucose from entering the hippocampal astrocyte cultures (43).

Finally, results showed that body weight decreased following the chronic stress (Fig. 7.A), a fact that can be well-explained by the stress-induced release of stress hormones (44). Brain and hippocampus weights, however, did not show any significant changes (Figs. 7.B and 7.C).

In conclusion, chronic stress, especially one without a recovery period, not only plays a major role in memory retention but also changes the IL-1 β and glucose levels, especially in blood serum. It appears that the time and duration of the induced stress are the two contributing factors as far as neurobiological responses are concerned. Furthermore, prolonged stress durations (over 21 days) can probably modulate the effects of chronic stress on the physiological system. Evaluation of molecular factors and gene expression, both of which are possibly involved in retention processes, are thus highly recommended for future research.

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