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Research report

Adverse effect of combination of chronic psychosocial stress and high fat diet on hippocampus-dependent memory in rats

K.H. Alzoubi[a], K.K. Abdul-Razzak[a], O.F. Khabour[b], G.M. Al-Tuweiq[c], M.A. Alzubi[a], K.A. Alkadhi[d,*]

[a] Department of Clinical Pharmacy, Facutly of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[b] Department of Medical Laboratory Sciences, Faculty of applied Medical Sciences, Jordan University of Science and Technology, Irbid, Jordan
[c] Department of Legal Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
[d] Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX 77204-5515, USA

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ABSTRACT

The combined effects of high fat diet (HFD) and chronic stress on the hippocampus-dependent spatial learning and memory were studied in rats using the radial arm water maze (RAWM). Chronic psychosocial stress and/or HFD were simultaneously administered for 3 months to young adult male Wister rats. In the RAWM, rats were subjected to 12 learning trials as well as short-term and long-term memory tests. This procedure was applied on a daily basis until the animal reaches days to criterion (DTC) in the 12th learning trial and in memory tests. DTC is the number of days that the animal takes to make zero error in two consecutive days. Groups were compared based on the number of errors per trial or test as well as on the DTC. Chronic stress, HFD and chronic stress/HFD animal groups showed impaired learning as indicated by committing significantly ($P < 0.05$) more errors than untreated control group in trials 6 through 9 of day 4. In memory tests, chronic stress, HFD and chronic stress/HFD groups showed significantly impaired performance compared to control group. Additionally, the stress/HFD was the only group that showed significantly impaired performance in memory tests on the 5th training day, suggesting more severe memory impairment in that group. Furthermore, DTC value for above groups indicated that chronic stress or HFD, alone, resulted in a mild impairment of spatial memory, but the combination of chronic stress and HFD resulted in a more severe and long-lasting memory impairment. The data indicated that the combination of stress and HFD produced more deleterious effects on hippocampal cognitive function than either chronic stress or HFD alone.

1. Introduction

Severe and/or long-term stress changes normal brain structure and function (reviewed in [1]). Among brain regions, the hippocampus is highly susceptible to adverse changes during repeated stress [2]. In the hippocampus, stress affects neuronal excitability, neurochemistry as well as structural and functional plasticity [1,3]. Chronic psychosocial stress is known to impair hippocampus-dependent forms of learning and memory in animal models [4–8] and in humans [9]. Moreover, chronic psychosocial stress exacerbates memory impairment during hypothyroidism [6] and in an animal model of Alzheimer's disease [8]. Stress also, markedly suppresses long-term potentiation (LTP), a widely accepted cellular correlate for learning and memory, in area CA1 of the hippocampus in adult anesthetized rats [7,10–17], and freely moving animals [18,19]. Similar findings were reported in hippocampal slices from stressed animals [20–27]. Chronic stress reduces the protein levels of essential signaling molecules associated with memory and LTP including phosphorylated CaMKII [8,12,15], and brain-derived neurotrophic factor (BDNF, [15,28,29]).

Diet is a major factor in maintaining neural and cognitive health throughout the lifespan of individuals. For example, high fat diet (HFD), that is rich in saturated fat and refined sugar, contributes to cognitive decline in aging and accelerates the course of dementia in Alzheimer disease [30,31]. Carbohydrates enriched HFD also aggravates impairment of cognitive functions following traumatic brain injury [32], cerebral ischemia/reperfusion injury [33] and intermittent hypoxia [34]. Even in normal animals, carbohydrates enriched HFD impairs learning and memory [35–39] and synaptic plasticity [39], by affecting BDNF and cyclic AMP-response element-binding protein (CREB, [36,40,41]). On the other hand, ketogenic diet i.e., low carbohydrate/high fat has a neuroprotective effect in Alzheimer's disease, Parkinson's disease, traumatic brain injury, epilepsy and stroke [42,43]. In older individuals, diets high in monounsaturated fatty acids and rich in fruits and fibers are associated with better memory scores and protection against cognitive decline [44–46].

Several studies have shown that combination of chronic stress and HFD consistently produces adverse effects on behavior and

* Corresponding author. Tel.: +1 713 743 1212; fax: +1 713 743 1229.
E-mail address: kalkadhi@uh.edu (K.A. Alkadhi).

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physiological responses other than learning and memory [47–51]. A recent study by Baran et al. [52] reported a synergy between HFD and stress leading to retraction of hippocampal dendrites, a process that is associated with impairment of learning and memory [53–56]. We, therefore, hypothesized that the combination of HFD and chronic stress could exert greater deleterious effect on learning and memory than either factor alone. In the current study, this hypothesis was tested on hippocampus-dependent learning and memory using the radial arm water maze (RAWM) paradigm.

2. Materials and methods

All experiments were carried out according to the ACUC Guidelines adopted by the Jordan University of Science and Technology. Young adult male Wister rats (b.w: 225–250 g) were housed on a 12/12 h light/dark schedule (lights on at 7 AM) in stainless steel cages (six rats per cage) at 25 °C with ad libitum access to rat chow and water. Animals were allowed 2 weeks to acclimate before experimental manipulations began. All experiments were performed between 8 PM and 5 PM.

2.1. Animal groups and diets

Among the 4 rat groups (control, stress, HFD, and stress/HFD), both the HFD and stress/HFD groups were fed only high fat diet containing (g%): 25% total fat (including 11% unsaturated fat), 44% carbohydrate, 18% protein, and 13% fiber, ash and other ingredients. The control and the stress groups were fed conventional diet, containing (g%): 5% total fat (including 2% unsaturated fat), 62% carbohydrate, 20% protein and 13% fiber, ash and other ingredients. In both diets, casein was the main source of protein. Butter and soybean oil were the main sources of fat, and starch was the main source of carbohydrates. Both diets contained similar amounts of omega fatty acids, standard vitamin and mineral mix with all essential nutrients. The diets were prepared at the animals care facility of the Jordan University of Science and Technology as described in the recommendation by the Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition, Board on Agriculture and National Research Council (1995) [57]. Diets composition was analyzed at the laboratories of the Royal Scientific Society (Amman, Jordan), a testing site accredited by the United Kingdom Accreditation Service. Food was provided ad libitum for the duration of the experiments. All manipulations including chronic stress, and HFD feeding were started on the same day (day 1 of the 3-months treatment), and continued throughout the behavioral testing days.

2.2. Induction of psychosocial stress

Both the stress and stress/HFD groups were stressed for 12 weeks. The chronic stress procedure was generated by daily random switching of two animals from one cage to the other. The procedure, termed "intruder" psychosocial stress, is known to generate highly reproducible stress; indicated by a significant increase in blood pressure [58] and glucocorticoids levels [11].

2.3. Radial arm water maze (RAWM) procedure

All 4 rat groups (control, stress, HFD, stress/HFD) were tested for learning and memory performance on the RAWM task. The RAWM is a black circular water-filled tub (water temperature: 24 ± 1 °C; dimensions: 167 cm diameter, height 55 cm, 43 cm deep) with six V-shaped stainless steel plates (49 cm height, 55 cm length) arranged to form a swimming field of an open central area and six arms (arm width 35 cm, [5–7,59–61]). Animals had to find a hidden platform (2 cm under water) at the far end of one of the swim arms (the goal arm). The goal arm was not changed for a particular rat in a single day but cannot be the same for a particular rat on two consecutive days. To avoid scent trail, no two animals, tested consecutively within the same day, had the same goal arm. Rats were allowed two blocks of six consecutive acquisition trials separated by 5 min resting time. The 12 trials were followed, 30 min later, by a short-term memory test and 5 h and 24 h later by long-term memory tests per day. Every trial/test was started in a different start arm (except the goal arm) in a particular day for a particular rat.

In each trial, the rat was allowed 1 min to swim freely in the maze to find the hidden platform. Once on the platform, the rat was allowed 15 s to observe visual cues before the next trial. Visual cues were available for the rats in fixed positions throughout the days of the experiments. When a rat was unable to find the platform within the 1 min period allowed, the experimenter guided it toward the platform for the 15 s stay. During the 1 min period, each time the rat entered an arm other than the goal arm, an error was registered. Entry was defined as the entry of the entire body of the rat including the tail into the particular arm. Training continued for all animals until they reached days to criterion (DTC) in the last acquisition trial and in all memory tests. DTC is the number of days the animal takes to make no error in two consecutive days. All experiments were carried out in a dimly lit room.

2.4. Statistical analysis

All statistics were carried out using the GraphPad Prism (4.0) computer program (GraphPad Software, La Jolla, CA). Comparisons were made using 1-way ANOVA test followed by Tukey posttest. $P < 0.05$ were considered significant. All values are represented as mean ± SEM

3. Results

The normal increase in body weight over the duration of the experiments in control and stress rats was 56–59%. However, HFD-fed animal groups (HFD and stress/HFD) showed significantly higher body weight gain (88–94%, $F_{(30,3)} = 87.97$, $P < 0.001$, $n = 8$–10 rats/group) than control and stress groups over the same time period (Fig. 1).

Using the RAWM, we have shown that 6 weeks of psychosocial stress impairs hippocampus-dependent spatial short-term memory only [6–8]. In present study, we tested the effect of 3-month chronic stress and/or HFD on spatial learning and memory formation. During the RAWM training, animals in all trials tried to escape the water and find the platform without showing any physical (movement or swimming) disability or reduced motivation (unwilling/unable to climb onto the platform, falling back into the water after climbing or swimming-still rather than searching for the platform). In the within-day learning task of the RAWM, all groups showed reduction in the number of errors on all days of training, as they learned during the acquisition (learning) phase (trials 1–12, Fig. 2A–E). On day 1 all animals showed poor performance because they were adapting to the procedure (Fig. 2A). On days 2 and 3, animal groups showed similar performance (trials 1–12, Fig. 2B and C). On the 4th day, stress, HFD, and stress/HFD groups made significantly more errors than the control group in trials 6 through 9 (Trial 6: $F_{(30,3)} = 5.18$, $P < 0.05$, Trial 7: $F_{(30,3)} = 8.49$, $P < 0.05$ Trial 8: $F_{(30,3)} = 8.69$, $P < 0.05$ Trial 9: $F_{(30,3)} = 5.65$, $P < 0.05$, $n = 8$–10 rats/group, Fig. 2D), indicating impaired learning caused by the 3-month chronic stress and/or HFD. On day 5 (Fig. 2E), all groups showed similar learning performance, and animals reached saturation point where number of errors reached the lowest possible level. By the end of the acquisition phase (trial 12) on all days, all groups learned to the same extent as suggested by similar number of errors made by all animal groups (Fig. 2A–E, $P > 0.05$, $n = 8$–10 rats/group). This indicated that stress and/or HFD slowed, but did not prevent the animals from ultimately learning the platform location.

The within-day memory tests of the RAWM showed that chronic stress and/or HFD impaired both short-term (30 min) and long-term memory (5 h and 24 h). In the short-term (30 min) memory

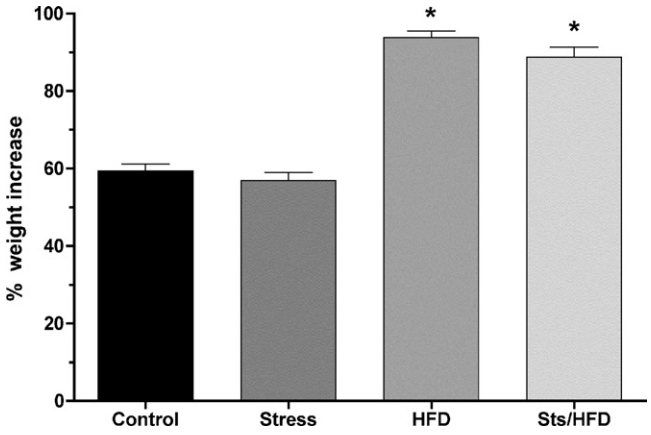

Fig. 1. HFD is associated with increase in body weight. Over the 3-month period, the percentage of increase in body weight was significantly more in the HFD and Sts/HFD groups than that of control or chronic stress groups. All values are mean ± S.E.M. (*) Indicates significant difference ($P < 0.001$, $n = 8$–10 rats/group) from the control value.

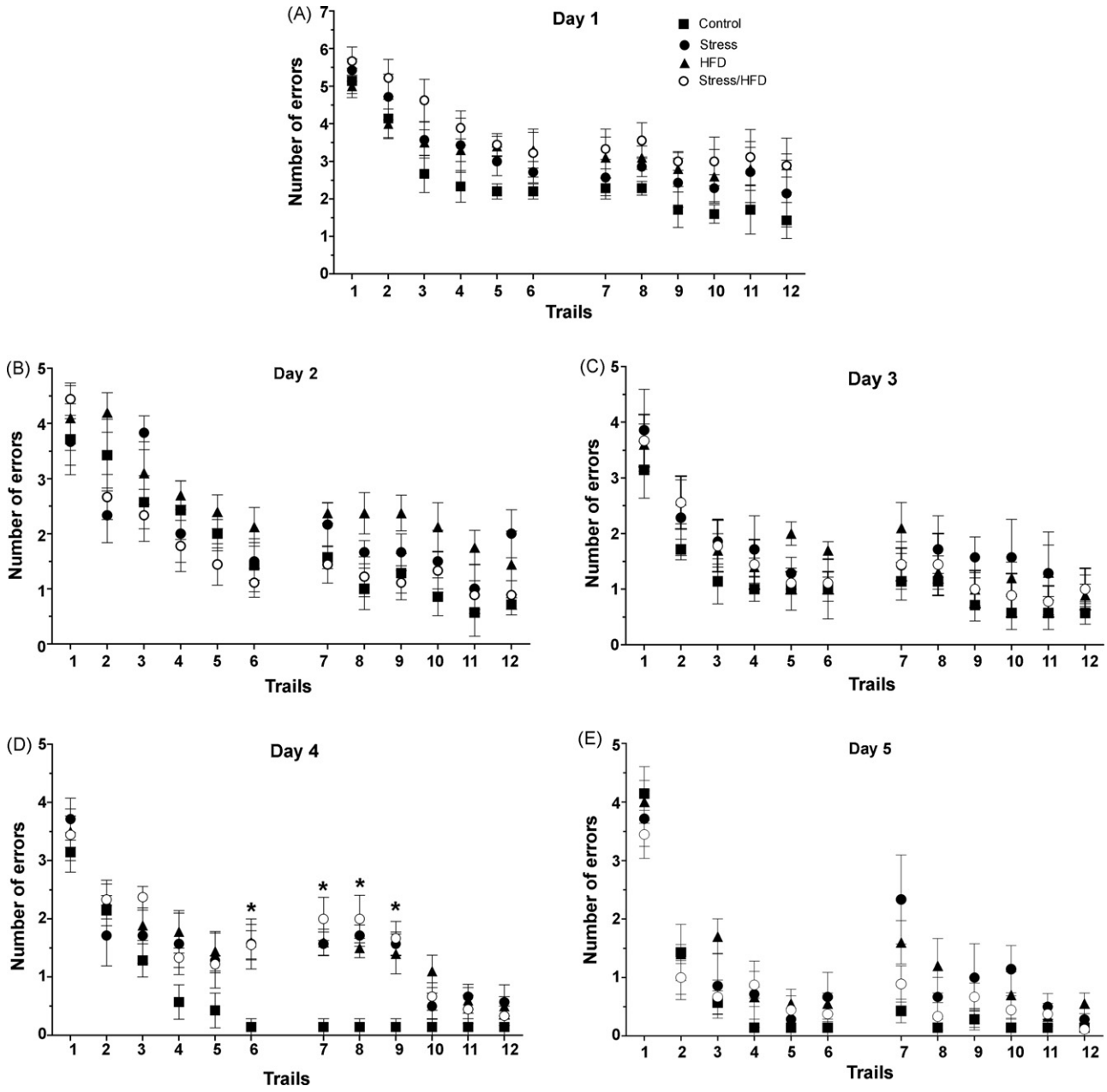

Fig. 2. Chronic, 3-month stress and/or HFD impair learning. (A) Shows the average errors committed by control, stress, HFD or stress/HFD groups in day 1 of the trials. Trials 1–12 indicate the learning curve. In (B), (C), (D) and (E) details are similar to (A) but for days 2–5, respectively. On days 1–3, all animal groups showed similar performance. On day 4, trials 6 through 9, animals in the stress, HFD and stress/HFD groups made significantly more error than the control group. On day 5, all groups showed similar learning performance. At this stage, animals reached saturation point where number of errors reached the lowest possible level. (*) Indicates significant difference ($P < 0.05$, $n = 8$–10 rats/group) from the control value.

test, stress, HFD and stress/HFD rats made higher number of errors compared to control group in days 1 through 4, indicating impaired short-term memory in these rats (Fig. 3A, day 1: $F_{(30,3)} = 5.32$, $P < 0.05$, day 2: $F_{(30,3)} = 6.0$, $P < 0.05$, day 3: $F_{(30,3)} = 6.9$, $P < 0.05$, day 4: $F_{(30,3)} = 5.1$, $P < 0.05$, $n = 8$–10 rats/group). Additionally, stress, HFD and stress/HFD groups made higher number of errors compared to control group in long-term memory tests of days 2 and 3 for the 5 h memory test (Fig. 3B, day 2: $F_{(30,3)} = 5.2$, $P < 0.05$, day 3: $F_{(30,3)} = 10.5$, $P < 0.05$, $n = 8$–10 rats/group), and days 3 and 4 for the 24 h memory test (Fig. 3C, day 3: $F_{(30,3)} = 11.5$, $P < 0.05$, day 4: $F_{(30,3)} = 6.5$, $P < 0.05$, $n = 8$–10 rats/group). In both the short-term (30 min) and 5 h long-term memory tests of day 5, the stress/HFD group made significantly more errors than the stress, HFD and control groups (Fig. 3A–C; 30 min test: $F_{(30,3)} = 5.32$, $P < 0.05$, 5 h test: $F_{(30,3)} = 14.1$, $P < 0.05$). No significant difference was observed among the stress, HFD, and control groups in all memory tests of day 5. These results suggest that HFD combined with chronic psychosocial stress caused more severe short-term and long-term memory impairment than rats in the stress or HFD groups.

The number of days rats needed to reach a performance criterion (days to criterion; DTC) was also recorded. In the DTC measure of the last trial of the acquisition phase (trial 12), no significant difference was observed among the groups (Fig. 4A, $F_{(30,3)} = 0.12$, $P > 0.05$, $n = 8$–10 rats/group), indicating that all rats learned to the same extent by the end of the 12 acquisition trials, thus, any defect observed in the memory testing is, in fact, due to actual memory impairment rather than failure to learn. The DTC values showed that chronic stress or HFD alone markedly impaired

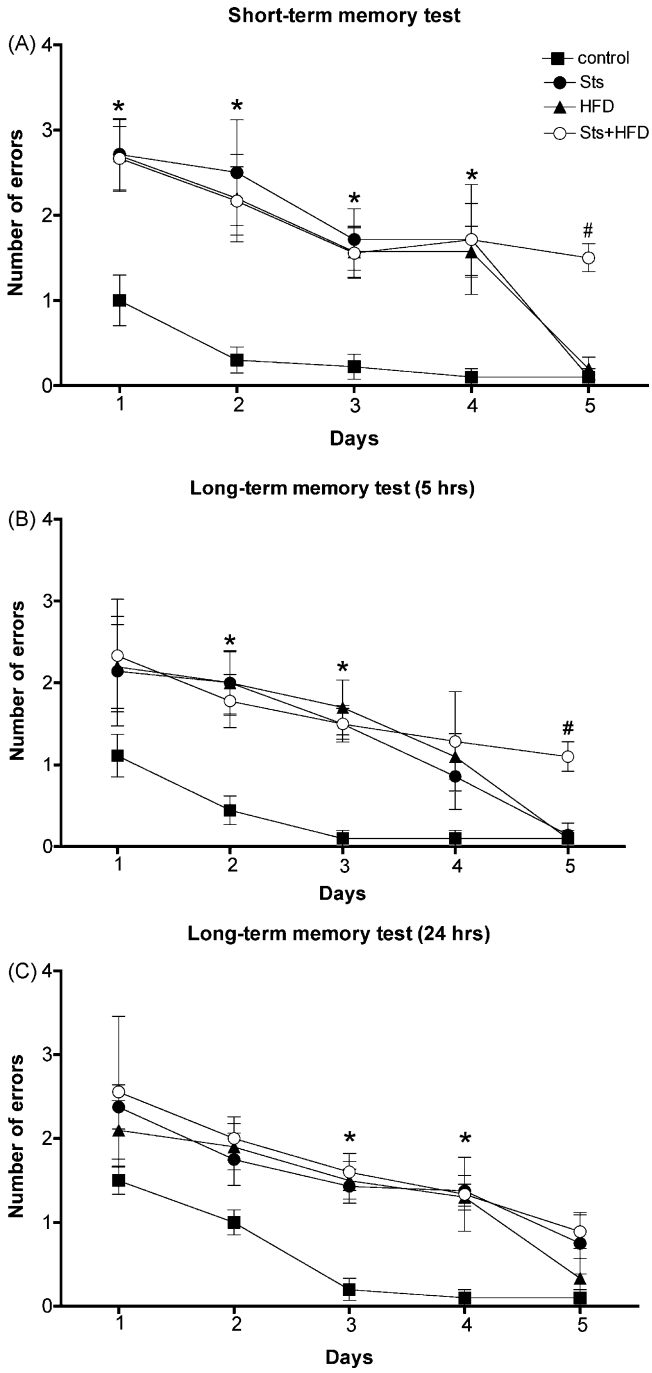

Fig. 3. Memory performance in the radial arm water maze (RAWM). Memory tests were performed 30 min (short-term memory) or 5 h and 24 h (long-term memory) after the last trial of the learning phase. Each point is the average values ± SEM from 8–10 rats. Chronic, 3-month stress and/or HFD impair short-term memory in days 1 through 4 (A), 5 h long-term memory in days 2 and 3 (B), and 24 h long-term memory test in days 3 and 4 (C). Combination of chronic stress and HFD impair short-term (A) and 5 h long-term (B) memory in day 5 more than either condition alone. (*) Indicates significant difference ($P < 0.05$) from the control value and (#) indicates significance difference ($P < 0.05$) of the combination from either condition alone.

short-term and long-term memory since stressed or HFD rats required significantly more days to reach the criterion than the control animals (Fig. 4B–D, 30 min test: $F_{(30,3)} = 26.7$, $P < 0.001$, 5 h test: $F_{(30,3)} = 22.5$, $P < 0.001$, 24 h test: $F_{(30,3)} = 16.8$, $P < 0.01$, $n = 8–10$ rats/group). Interestingly, the DTC measure showed that stress/HFD group needed significantly more days to reach the criterion in short-term (Fig. 4B; 30 min test: $F_{(30,3)} = 26.7$, stress vs stress/HFD: $P < 0.05$, HFD vs stress/HFD: $P < 0.01$, $n = 8–10$ rats/group) and long-term memory (Fig. 4C and D, 5 h test: $F_{(30,3)} = 22.5$, stress vs stress/HFD: $P < 0.05$, HFD vs stress/HFD: $P < 0.01$, 24 h test: $F_{(30,3)} = 16.8$, stress vs stress/HFD: $P < 0.05$, HFD vs stress/HFD: $P < 0.01$, $n = 8–10$ rats/group) compared to the days needed for stress or HFD alone groups. These results indicate that combination of chronic stress and HFD exert more severe short-term and long-term memory impairment than either condition alone.

4. Discussion

Chronic stress and high fat diet are conditions that adversely affect cognitive functions. In this study, we evaluated the effects of these two conditions in the RAWM, a hippocampus-dependent memory task. Our findings indicate that high fat diet combined with chronic stress impairs memory more severely than either condition alone.

The behavioral model used in this study to test learning and memory, the RAWM design [5,59] resembles a radial arm maze inserted into a Morris maze (a circular tank filled with water). Conditions that adversely affect hippocampal function such as aging [62], Alzheimer's disease [8], chronic or acute stress [5–7,59,63,64], hypothyroidism [6,60,61] or the combination of chronic stress and hypothyroidism [6] impair RAWM performance. On the other hand, drugs with known neuroprotective effect on the hippocampus (e.g. nicotine and thyroxin) were shown to normalize stress- and hypothyroidism-induced impairment of RAWM performance [60,61]. Consistent with previous studies, the present experiments revealed impaired short-term memory in the stressed animals [6–8]. We have previously demonstrated that stress impairs early LTP (E-LTP), a putative correlate of short-term memory, possibly as a result of decreased CaMKII and PKC levels in the hippocampus [8,11,12,15].

Interestingly, results of this study show that chronic stress slows learning and impairs long-term memory formation. The impairment of learning and long-term memory in rats that were stressed for 3 months was unexpected, given that our previous studies using the RAWM did not detect learning and long-term memory impairment due to shorter duration (4–6 weeks) of chronic stress [8,11,12,15]. However, in this study, extending chronic stress duration to 3 months, caused impairment of both short-term and long-term memory. Other forms of stress have been shown to impair long-term memory [65–68], which is in line with the current findings.

Chronic psychosocial stress is commonly encountered in modern societies, particularly the highly prevalent work-related stress or that arising from socioeconomic disadvantage and discrimination. Stress affects both the structure and function of the hippocampus. Dendritic atrophy, suppression of neurogenesis and cell death in the hippocampus have been attributed to chronic stress [1,3,52]. Antagonists of the *N*-methyl-D-aspartate (NMDA) receptors can prevent or reverse hippocampal neuronal atrophy [69], and administration of the tianeptine, an antidepressant that normalizes stress effects on NMDA channel currents [70,71], blocks the adverse effects of stress on LTP and hippocampal morphology [71–73].

Life style and related dietary habits play an essential role in maintaining neural health throughout the life span of individuals. Diet rich in saturated fat and refined sugar (HFD), typical of most industrialized western societies [74], can contribute to cognitive decline during various conditions such as aging [75,76], Alzheimer's disease [30,31], traumatic brain injury [32], cerebral ischemia/reperfusion injury [33] and intermittent hypoxia [34]. Results of this report are consistent with these studies in showing that HFD impairs normal memory and exacerbates chronic stress-induced memory impairment.

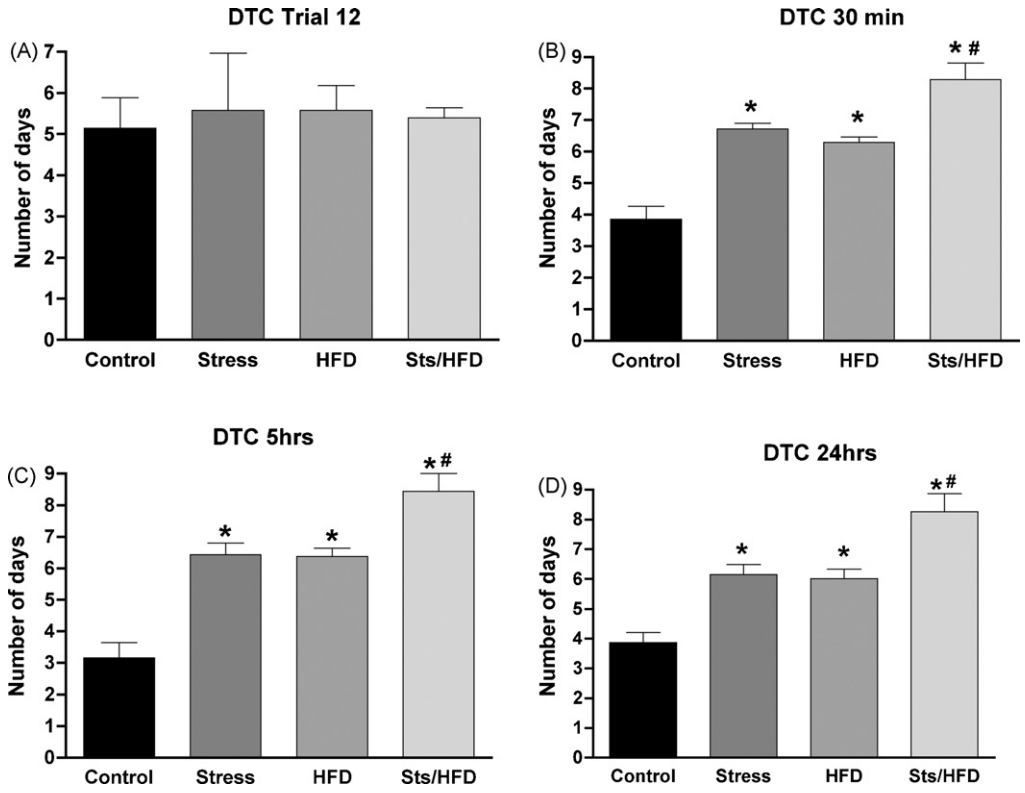

Fig. 4. The combination of stress and HFD impairs short- and long-term memory more than either condition alone. Days to criterion (DTC) are plotted for trial 4 (A: learning), Test at 30 min (B: short-term memory) and tests at 5 h and 24 h (C and D: long-term memory). DTC is a standard criterion in which, the performance is flawless in two consecutive days of testing in any of these trials (see Methods). (*) Indicates significant difference ($P < 0.05$) from the control value and (#) indicates significance difference ($P < 0.05$) of the combination from either condition alone.

The exact mechanism for HFD-induced cognitive impairment is currently unknown. It has been assumed that the effects of HFD on neural function result primarily from cardiovascular dysfunction such as atherosclerosis [77]. It is known that daily diet provides an immediate energy source for the brain because the brain can neither synthesize nor store its own energy reserves. Moreover, HFD reduces brain-derived neurotrophic factor (BDNF) in the hippocampus and this decrease is associated with reduced cognitive performance [36,40,41]. Similarly, chronic stress-induced cognitve impaitment was associated with reduced hippocampal BDNF [15]. Therefore, it is likely that reduction in BDNF neurprotective functions represent a common mechanism for cognitive impairment in both HFD and chronic stress.

Like either condition alone, the combination of HFD and stress slowed, but did not impair learning. However, the combination impaired short-term as well as long-term memory more than either condition alone. This result supports previous reports, which show synergistic effects for HFD and chronic stress on hippocampal neurons atrophy [52], and other physiological measures, including elevation in plasma catecholamine levels [48] and increase in stress-induced mortality and cardiovascular disorders [47,49]. Epidemiological studies also indicate that HFD or stress produces a relatively mild effect on health and well being ([78,50,51]), while the combination of a stressful life and HFD exerts a more serious adverse effect [51,79]. The basis for the synergy between HFD and chronic stress on cognitive functions require further investigation. However, it can be at least partly attributed to increased reactivity of the hypothalamic pituitary adrenal (HPA) axis to stress, when animals are fed HFD. In that respect, dietary fat is suggested to work as a background inducer leading to exaggerated corticosterone and HPA axis responses during chronic stress [80].

The high fat diet (HFD), used in the current study is also rich in carbohydrates, and has negative effects on neural functions especially learning and memory. In contrast, ketogenic diet that has high fat content, but low carbohydrate, has a neuroprotective effect in Alzheimer's and Parkinson's disease, traumatic brain injury, and stroke (reviewed in [42]), and protects against cognitive impairment in epilepsy (reviewed in [43]). Moreover, several studies indicate that ketogenic diet may be associated with long-lasting therapeutic benefits for patients with in epilepsy (reviewed in [42]).

Body weight gain did not change as a result of the intruder model of chronic psychosocial stress used in this study. This in agreement with previous reports from our laboratory (e.g. [11,6,12]) and others [64]. However, different forms of stress have been shown to induce reduction of weight gain [5,52]. Additionally, results of this study showed that HFD for 3 months increased weight gain compared to LFD, which is in agreement with previous reports (e.g. [81]). However, other studies in which HFD was instituted for only 3 weeks, reported no significant change in weight gain (e.g. [52]). This difference in duration of HFD may very likely explain the dissimilar results among studies. Moreover, the increased body weight gain in HFD animals, shown in this study, could be due to increased body fat as a result of increased dietary fat content or due to increased caloric content in HFD. Finally, it is very unlikely for increased weight of HFD animals to cause impaired maze performance, because the mobility and motivation of animals appeared to be unaffected.

In summary, we have shown that HFD or stress delay hippocampus-dependent spatial learning and impair memory tested in the RAWM, and the combination of the two conditions has a more deleterious effect on memory than either condition alone.

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