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Fluoxetine abolished psychological stress deleterious effect on memory in protein malnourished mice

Sabry M. F.[a*], Hamed M. R.[a], & El-sayed M. E[b]

[a] Department of pharmacology, National organization for drug control and research, Cairo, Egypt. [b] Department of pharmacology and toxicology, Faculty of pharmacy, Cairo University, Egypt.

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ABSTRACT

The aim of the present study is to investigate the effect of Fluoxetine (FLX) on both learning and memory of psychologically stressed protein malnourished mice as compared to its effect in normally fed ones. Animals were divided into two major groups, a normally fed (NF) mice and a Protein malnourished one (PM). Stress was induced using the learned helplessness (LH) technique. Each animal was exposed for 5 days to the psychological stress session alone or in association with drug administration following completion of 21 days under the diet regimen. Fluoxetine (FLX) was administrated daily in dose of 10mg/kg i.p. before mice exposed to foot shocks. Stress significantly decreased time required to reach platform in normally-fed (NF) mice. FLX significantly increased time required to reach platform as compared to (PM) escape mice. Stress significantly decreased time spent in platform quadrant in both (NF) and (PM) mice. FLX significantly increased time spent in the platform quadrant, as compared to stressed (PM) mice. The results could be concluded that stress enhanced learning in (NF) mice and impaired memory in both (NF) and (PM) mice. FLX abolished psychological stress effect on memory performance under protein malnutrition. Fluoxetine retard learning in (PM) escape mice. Such effects were correlated with significant modifications of brain 5-HT, NE and DA contents.

INTRODUCTION

Stress is the physiological, psychological and behavioral response by individuals when perceive a lack of equilibrium between the demands placed upon them and their ability to meet those demands. Stress over a period of time leads to ill-health Palmer (1989). Stress can be induced physically or psychologically. Learned helplessness (LH) is used to induce psychological stress. LH refers to a condition of a human person or an animal which had learned to behave helplessly, even when the opportunity is restored to help their self by avoiding unpleasant circumstances to which they have been subjected (Bhatia *et al*, 2011). LH is a paradigm in which animal is exposed to repeated uncontrollable electric shocks followed by controllable shocks but the animal become helpless (Chourbaji *et al.,* 2005)**.** Different stress stimulations have different effects on learning and memory. Experimental studies showed that stress induce learning and memory impairment (Kim *et al.,* 2001 and Song *et al.,* 2006), while others have shown that stress induce enhancement of learning and memory (Xiao-Heng *et al*., 2007 and Chen-you *et al*., 2006). Learning and memory components of spatial navigation in rodents rely on hippocampal synaptic plasticity (Shapiro and Eichenbaum, 1999&Martin and Morris, 2002). Stress or elevated GC levels have inverted-U effects on hippocampal synaptic function and spatial learning. For instance, a mild stressor or moderate GC levels improves spatial memory (Akirav *et al*., 2004). Conversely, chronic stress or increased GC levels impairs spatial memory (Luine *et al*., 1994).

Protein Malnutrition (PM) is a fatal body-depletion disorder and is considered the most important risk factor for illness and deaths through the whole world especially in the developing countries. PM is known to be developed in children and adults where consumption of protein and energy is insufficient to satisfy their needs. Pure protein deficiency can occur when the body is provided with sufficient energy but lacks the amount required of protein (Haggerty, 2006). Several studies revealed that PM impairs cognitive function through decreasing hippocampal BDNF concentration (Wang and Xu, 2007) or by a dysfunction of the cholinergic neurons in the hippocampus (Nakagawasai *et al*., 2006).

* *Corresponding Author*
Fatma Sabry, Email: fatmasabry@ymail.com
Tel.: +20 1277510241

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Fluoxetine is widely used as an antidepressant. Several studies showed that FLX inhibited the immobility period (Dhir and Kulkarni 2008) and increased climbing without affecting swimming in forced swim test in congenitally helpless rats (Shumake *et al.*, 2010). FLX acts through selective inhibition of serotonin reuptake (Bendele *et al.*, 1992).

We have not found in the previous literatures any study that investigates the effect of fluoxetine on psychological stress under protein malnutrition. The goal of this study is to investigate effect of fluoxetine on both psychological stress and protein malnutrition consequences concerning learning and memory.

MATERIALS AND METHODS

Animals

Adult male Swiss mice weighing 20-25 grams were used. Animals were obtained from animal house of National Organization for Drug Control and Research. The animals were caged six animals under conventional laboratory conditions and free access to food and water one week for accommodation. Ten animals were used in each group.

Drugs

Fluoxetine Hcl was obtained from El Nile Company, Egypt.

Diet Preparation

The standard diet was prepared according to **(**Bamji, and Sharada 1972**)** as normal nourished mice were subjected to a diet containing 20% casein, while protein malnourished mice were fed a diet that contains 8% casein (Hassanein and Hamed, 2008).

Experimental design

Animals were divided into two major groups: a normally fed group (NF) and a protein malnourished (PM) group. NF mice were fed diet containing 20% protein while PM mice were fed diet containing 8% protein diet (PM) for 21 days. After completion of 21 days under the prepared diet regimen each group was divided into:

1. **Normal control (i.p.)**: Animals received saline i.p.
2. **Escape control (i.p.)**: Animals received saline i.p.+ 30 escapable foot shocks
3. **FLX+ Escape control (i.p.)**: Animals received FLX (10mg/kg i.p.)+ 30 escapable foot shocks**.**
4. **Stress control**: Animals received 60 inescapable foot shocks for 4days followed by 30 escapable foot shocks in 5^{th} day.
5. **FLX+ stress**: Animals received FLX (10mg/kg i.p.)+60 inescapable foot shocks for 4days followed by 30 escapable foot shocks in 5^{th} day.

Behavioral evaluation

Experimental animals were subjected to LH test. MWM training was applied for 3 days 24 hour after LH test. A probe test, test for memory, was conducted after last training day by 24 hour. Animals were monitored by a video camera for assessment of the behavioral parameters namely time required to reach platform and time spent in the platform quadrant.

Learned helplessness

Learned helplessness device consist of:

- A transparent Plexiglas shock chamber (18 - 18 - 30 cm^3), equipped with a stainless steel grid floor (diameter of each grid: 0.5 cm, spacing: 0.6 cm).
- The shuttle box consisted of equal sized compartments (18- 18 -30 cm^3) that were separated by a small gate (diameter of each grid: 0.5 cm, spacing: 0.6 cm). Both compartments of the shuttle box contained a grid floor. One compartment received electric current whereas another is considered as a safety area; not receive the current (Reif *et al.*, 2004).

Experimental animals were subjected to 60 inescapable foot shocks trials of 0.2mA for15 seconds with 5 seconds intertrial interval for 4 days where no chance for escape (training session). After 24h of last training day 30 escapable foot shocks trials of 0.2mA for 3 second with 10 seconds intertrial interval (test session).

MWM test

This test is used to evaluate spatial learning and memory where each mouse learns to swim in circular pool of water to find submerged platform then after platform removal mouse freely swim searching for the missing platform (Lione *et al.*, 1999). Morris water maze (MWM) is circular plastic pool of 61cm diameter with constant cues external to the maze and contain platform of 5cm diameter in a fixed position in one quadrant of the tank and submerged 1cm below the surface of the water. Water is made turbid using starch (Mean *et al.*, 1993). In the training session the experimental animal was subjected to four trials per day for three days. The stating position of each trial is randomized between four possible positions (N, S, E, and W). The location of platform remained constant through training session. A maximum of 60 s was allowed during the animal had to find the platform and climb onto with intetrial interval was 10-15 seconds. If the animal fails to reach platform it was put on the platform for 10 second. On fourth day the probe test was carried out by removing platform and placing the animal in starting position that facing quadrant that originally contained the platform and allows swimming for 60 s (Mean *et al.*, 1993)**.**

Neurochemical studies

Animals after LH test session were decapitated. DA, NE and 5-HT were estimated spectrophotoflurometrically.

Statistical analysis

Data were expressed as mean and standard error. Comparisons between different treatments were carried out using

one way analysis of variance (ANOVA) followed by LSD according to (Armitage and Berry, 1987).

RESULTS

Induction of stress didn't affect learning ability under protein malnutrition. However, stress under normal feeding condition significantly decreased time required to reach platform by 43% ($p \leq 0.001$) as compared to escape control saline i.p. Escape controls increased the time required to reach platform, as compared to normal control, under normally fed conditions. Protein malnutrition decreased time required to reach platform, as compared to normally fed corresponding control. FLX treatment increased time required to reach platform by 62% ($p \leq 0.05$) as compared to escape control saline i.p. under protein malnutrition condition. fig (1, A & B).

Combination of stress and protein malnutrition caused significant decrease in the time spent in the platform quadrant by 15% ($p \leq 0.05$) as compared to stressed normally fed mice. FLX treatment in stressed protein malnourished mice caused significant increase in time spent in the platform quadrant by 21% ($p \leq 0.05$) as compared to stressed protein malnourished mice. Fig (2, A& B).

Stress caused a significant decrease in the whole brain contents of DA, 5-HT and NE under both diet regimens as compared to escape and normal controls. Protein malnourished mice showed significant increase in DA whole brain content as compared to normally–fed ones.

Protein malnourished stressed mice showed significant increase in 5-HT and NE whole brain content as compared to normally –fed stressed ones. FLX treatment lowered DA, NE and 5-HT whole brain contents as compared to stress normally- fed mice. However, FLX didn't affect DA whole brain content in stressed protein malnourished mice. FLX significantly decreased DA whole brain content under both diet regimens as compared to their controls.

In escape mice, FLX significantly increased 5-HT and NE whole brain content under both diet regimens as compared to their controls.

FLX treatment in presence of stress caused significant decrease in 5-HT and NE whole brain contents, as compared to stressed mice under normal feeding condition. FLX has no significant effect on 5-HT and NE whole brain contents in stressed protein malnourished mice. Fig (3,4 & 5, A & B).

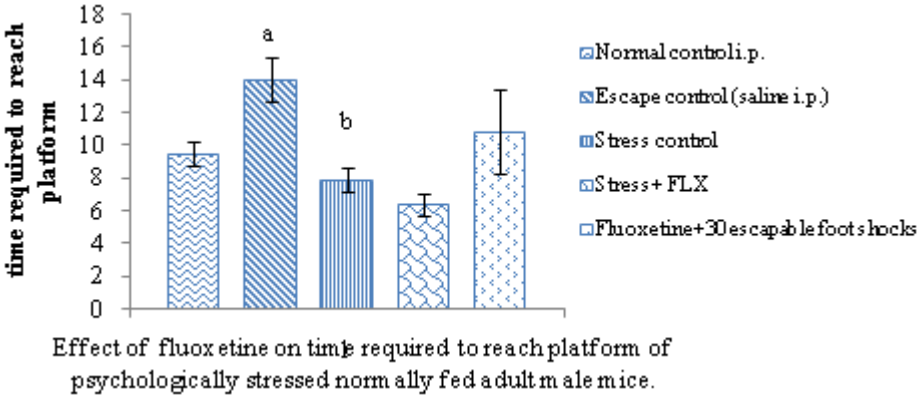

Fig. (1, A): Effect of fluoxetine (FLX) on time required to reach platform of psychologically stressed normally-fed mice.
a: significantly different from normally- fed normal control i.p. at $p < 0.05$ b: significantly different from normally- fed escapable control i.p. at $p < 0.05$

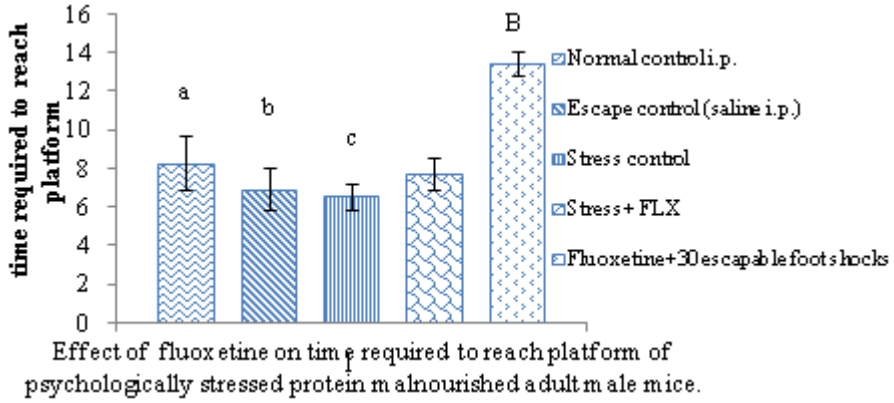

Fig. (1, B): Effect of fluoxetine (FLX) on time required to reach platform of psychologically stressed protein malnourished mice.
a: significantly different from normally- fed normal control i.p. at $p < 0.05$ b: significantly different from normally- fed escapable control i.p. at $p < 0.05$
B: significantly different from protein malnourished escapable control i.p. at $p < 0.05$ c: significantly different from normally- fed stress control at $p < 0.05$

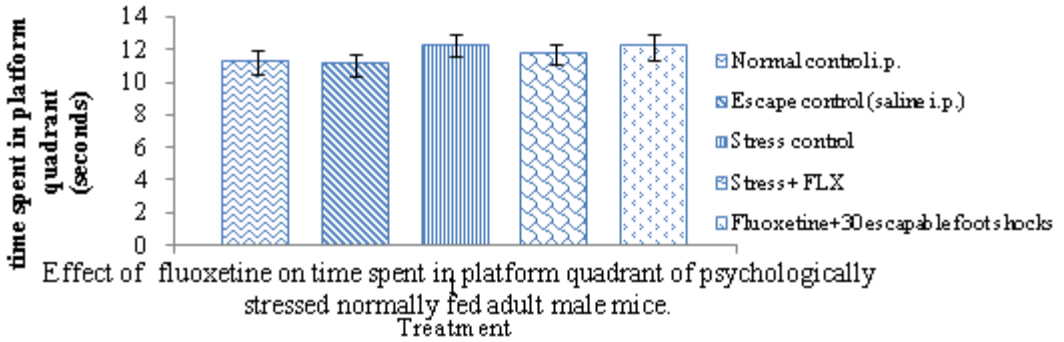

Fig. (2, A): Effect of fluoxetine (FLX) on time spent in the platform quadrant of psychologically stressed normally-fed mice.

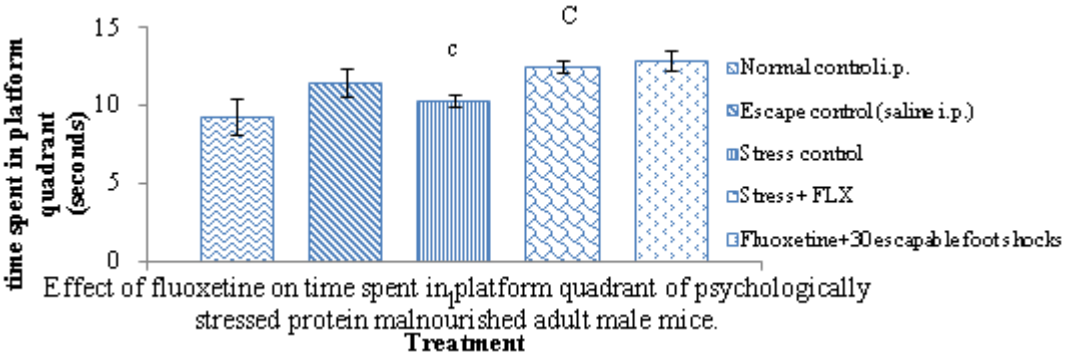

Fig. (2, B): Effect of fluoxetine (FLX) on time spent in the platform quadrant of psychologically stressed protein malnourished mice.
c: significantly different from normally -fed stress control at p< 0.05
C: significantly different from protein malnourished stress control at p< 0.05

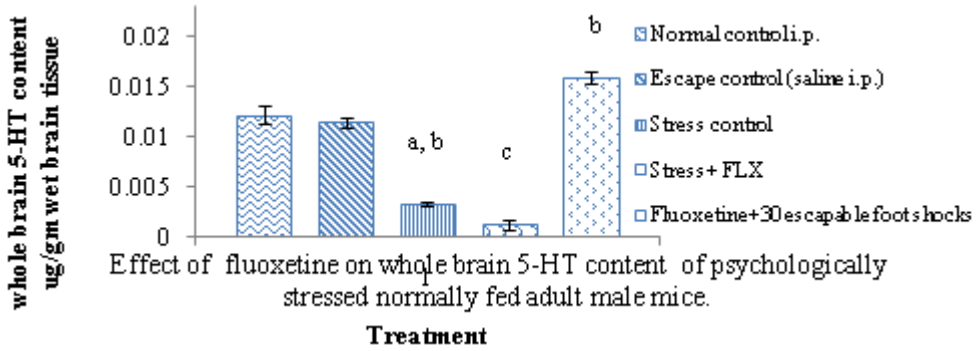

Fig. (3, A): Effect of fluoxetine (FLX) on whole brain 5-HT content of psychologically stressed normally-fed mice.
a: significantly different from normally- fed normal control i.p at p< 0.05
b. significantly different from normally- fed escapable control i.p. at p< 0.05
c: significantly different from normally- fed stress control at p< 0.

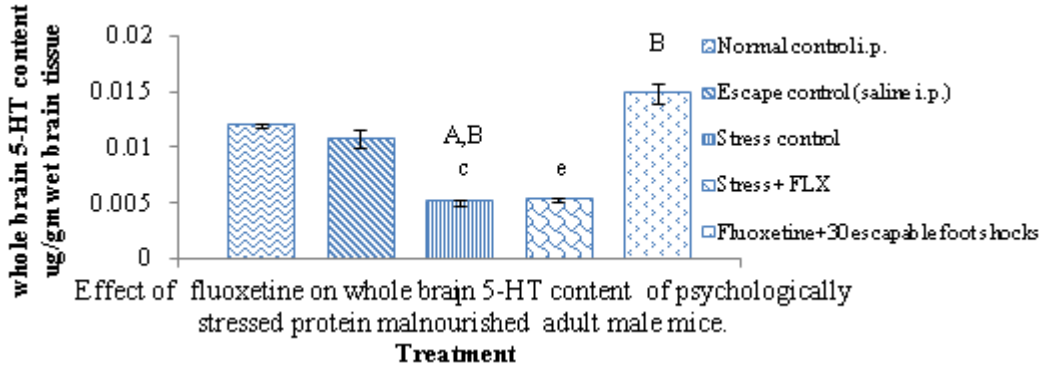

Fig. (3, B): Effect of fluoxetine (FLX) on whole brain 5-HT content of psychologically stressed protein malnourished mice.
c: significantly different from normally- fed stress control at p< 0.05
A: significantly different from protein malnourished normal control i.p at p< 0.05
B: significantly different from protein malnourished escapable control i.p. at p< 0.05
e: significantly different from normally- fed stress+ FLX at p< 0.05

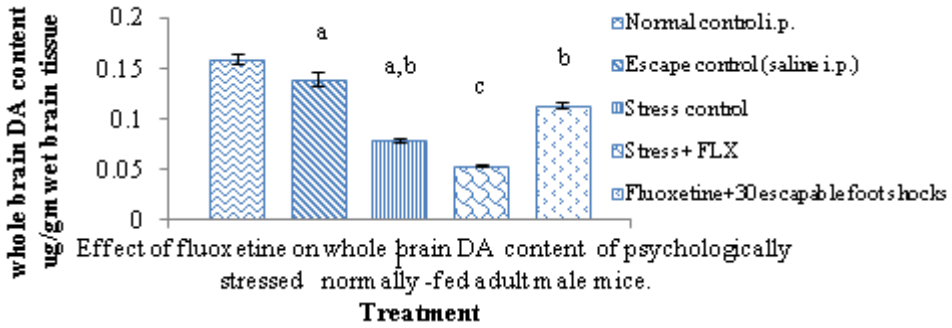

Fig. (4, A): Effect of fluoxetine (FLX) on whole brain DA content of psychologically stressed normally-fed mice.
a: significantly different from normally- fed normal control i.p at p< 0.05; **b:** significantly different from normally- fed escapable control i.p. at p< 0.05
c: significantly different from normally- fed stress control at p< 0.05

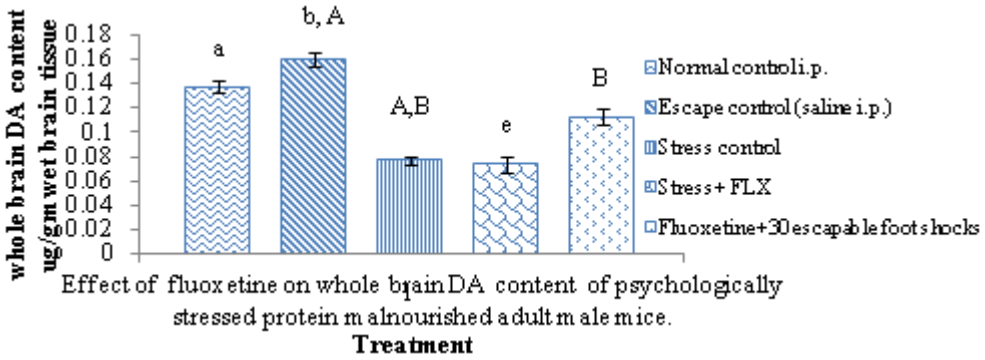

Fig. (4,B): Effect of fluoxetine (FLX) on whole brain DA content of psychologically stressed protein malnourished mice.
a: significantly different from normally- fed normal control i.p at p< 0.05;
A: significantly different from protein malnourished normal control i.p at p< 0.05;
b: significantly different from normally- fed escapable control i.p. at p< 0.05;
B: significantly different from protein malnourished escapable control i.p. at p< 0.05; **e:** significantly different from normally- fed stress+ FLX at p< 0.05

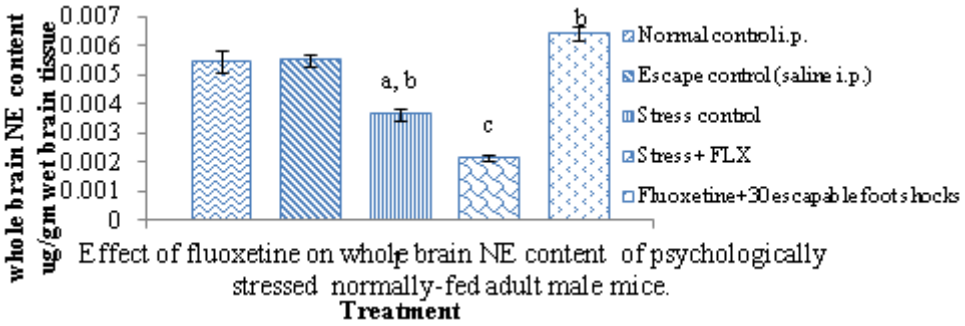

Fig. (5, A): Effect of fluoxetine (FLX) on whole brain NE content of psychologically stressed normally-fed mice.
a: significantly different from normally- fed normal control i.p at p< 0.05
c: significantly different from normally- fed stress control at p< 0.05
b: significantly different from normally- fed escapable control i.p. at p< 0.05

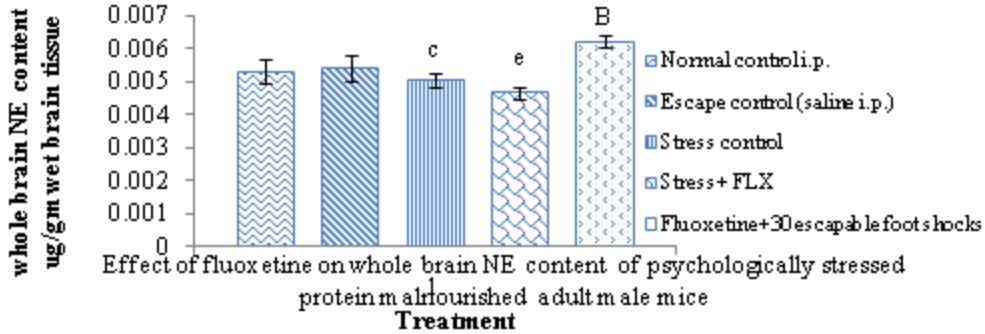

Fig. (5, B): Effect of fluoxetine (FLX) on whole brain NE content of psychologically stressed protein malnourished mice.
e: significantly different from normally- fed stress+ FLX at p< 0.05
B: significantly different from protein malnourished escapable control i.p. at p< 0.05
c: significantly different from normally- fed stress control at p< 0.05

DISCUSSION

In the present study stress significantly decreased time required to reach the platform as compared to normally fed control mice, thus stress enhance learning. this agrees with studies in which Chronic multiple stress enhance spatial learning as it decreased escape latency through increase expression of Fyn(regulatory protein which participates in synaptic plasticity, Brain-derived neurotrophic factor (BDNF) and TrkB proteinsthe (primary signal transduction receptor for BDNF) and the level of Fyn mRNA in hipocumppus (Xiao-Heng *et al* ., 2007) and through increased levels of CaMKII, CaM mRNA, and CREB mRNA (Chen-you *et al*., 2006). It well known that integrity of hippocampal formation is essential for spatial learning and memory (D'Hooge and Deyn, 2001), another study showed that predator odor which is a psychological stress enhance spatial learning in Morris water maze through co-activation of the amygdala–hippocampal pathways (Galliot *et al*., 2010). On the other hand, the present results are not in agreement with those obtained by (Warner and Drugan, 2010). The observed controversy could be attributed to application of different type of stress, where the author used intermittent swim stress and different species of animals used where the author used rats not mice. The obtained results revealed that, protein malnutrition decreased time required to reach platform in acquisition phase in MWM. This could be attributed to increase in whole brain DA content caused by protein malnutrition. Dopamine is involved in learning process as dopamine D1 receptor knockout mice show learning deficit (El-Ghundi *et al*., 1999) and systemic administration of D1-like receptor antagonist SCH23390 and D2-like receptor antagonist sulpiride prolong escape latency in MWM (Stuchlik *et al*., 2007). Several studies investigate the effect of protein malnutrition on learning and prove that protein malnutrition has adverse effect on learning in MWM (Wang and Xu, 2007 &Fukuda *et al*., 2007). In the current study fluoxetine significantly increase time required to reach platform in escape protein malnourished mice as compared to control. this result suggests that the serotoninergic system was affected by malnutrition. This effect is in agreement with the finding of (Barreto *et al.*, 2004) where fluoxetine treatment reduced aggressive response in well-nourished but not in malnourished rats. The present result is not in complete agreement with the data obtained by (Valluzzi and Chan, 2007) who reported that fluoxetine exerted different effect on learning as it didn't affect a spatial learning task (hippocampal-dependent) while it impairs the hippocampal-independent task (short-delay appetitive Pavlovian-conditioning task and an object-recognition task) the difference may be due to fluoxetine has different effects on different brain regions and as learning is not a unitary phenomenon, it may be the case that fluoxetine has different effects on different types of learning and paradigms. In the current study stress decreased swimming time in platform quadrant in both normal feeding and protein malnutrition conditions. These results are in agreement with Quervain *et al.*, (1998), Kim *et al.*, (2007) and Li *et al.*, (2009) a. Similarly the results coincide with the finding reported by (Pei Ma *et al.*, 2007) and (Cui *et al.*, 2009). Thus stress impairs memory. Such result may be attributed to the fact that stress lowers NE content. In the current study protein malnutrition decrease time spent in platform quadrant. Such a decrease agrees with the data obtained by (Valadares *et al.*, 2010), (Bayat *et al.*, 2005) and (Lukoyanov and Andrade;2000). The present finding indicates that protein malnutrition has deleterious effect on memory that is exacerbated in presence of stress. The poor memory performance could be explained on parallel lines mentioned by (Wang and xu, 2007) where protein malnourished rats showed decreased hippocampal BDNF concentration or by (Soto-Moyano *et al.*, 2005) where protein malnourished animals have over expression of neocortical α2c-adrenoceptors. In the current study fluoxetine treatment in presence of stress increased time spent in platform quadrant as compared to stressed protein malnourished mice, thus fluoxetine enhances memory. This result agree with several studies, i.e. Flood and Cherkin, (1987), Jin *et al.*, (2009) and Li *et al*., (2009) b. In the present study fluoxetine which is selective 5-HT reuptake inhibitor enhance memory due to increasing whole brain 5-HT content. This view is emphasized by (Kim *et al.*, 2011) who reported that treadmill exercise increased 5-HT synthesis in the dorsal raphe, which, in turn enhanced BDNF expression in the hippocampus, resulting in the restoration of memory function.

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