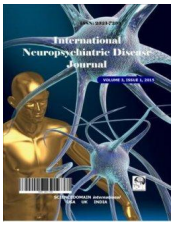

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Assessment of Improvement in Feeding Behavior and Co Morbid Psychiatric Disorders in Morphine Addiction Period in Socialized Male Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author HF designed the study and wrote the protocol with assistance from author MK. Author HF preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with assistance from author MK. Author FA mainly helped through preparing histological sections for immunostaining. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: In previous studies, other function of adult hippocampal neurogenesis besides memory and learning has not been studied. The aim of this study is to discover other function of hippocampal neurogenesis, especially in addiction period.
Materials and Methods: In this experiment 48 male Sprague-Dawley were randomly divided in four groups: 1) socialized 2) isolated 3) addicted socialized rats 4) addicted isolated rats. At the end of experiments short term memory, feeding behavior, blood glucose, zinc, anxiety level and neurogenesis were assessed.

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Results: Short term memory was impaired in addicted isolated rats compared to addicted socialized rats. Food consumption increased in addicted social rats compared to addicted isolated rats. Level of blood glucose increased in addicted socialized rats compared to addicted isolated rats. Anxiety level increased in addicted isolated rats compared to addicted socialized rats. Neurogenesis decreased in addicted isolated rats compared to addicted socialized rats. Zinc was elevated in addicted isolated rats compared to addicted socialized rats.
Conclusion: Feeding behavior can be regulated by adult hippocampal neurogenesis in addiction period, and socialization improves it. Also along with these positive effects co morbid psychiatric disorder such as an anxiety improves in addiction period.

Keywords: Neurogenesis; memory; Y-maze; anxiety; addicted; zinc and glucose.

1. INTRODUCTION

Contrary to earlier dogma, it is now acceptable that adult brain is capable of generating new neurons [1]. Adult neurogenesis predominantly occurs in two regions of brain; subventricular zone and subgranular zone of hippocampus [2]. Newly generated neurons are involved in tuning the hippocampus to changing environment [3]. These changes may help in improving rewarding experiences or facilitate the avoidance of stressful conditions [4]. It is believed that there is a balance between positive and negative reinforcing states and, any disbalance may result in mood imbalances like anxiety and depression [5]. In addition, neuronal loss can lead to memory impairment as assessed by Morris water maze [6]. Since neurogenesis should be activated in quiescent neurons. In subventricular zone in is promoted by injury, ischemia and infarction [7] and from this area they are migrating to olfactory bulb where they differentiate into granule and periglomerular cells [2]. There are growing evidences that link energy balance and food intake to adult hippocampal neurogenesis [8].

Socialization promotes new habits and skills in individuals [9]. Social interaction is especially important during childhood as it facilitates learning, reasoning, comprehension and critical thinking [10]. In addition, adult socialization helps in acquiring new values and behaviors associated with new adult statuses and roles. Environmental enrichment is more powerful than socialization in strength for activating neurogenesis [11]. In contrast, social isolation during adulthood can bring about a variety of troubles like personality disorder, family instability and social problems [12]. Social isolation impairs learning and memory formation, and promotes mood disturbances [13].

Feeding behavior is a habit that regulated by many mechanisms. But the exact regulatory mechanisms are not well understood. Feeding behavior is a complex behavior that is regulated by hypothalamus [14]. It is regulated by hormonal and paracrine factors. Studies in this context for role of hippocampus are growing. Some studies have proved it for regulation of food intake [15]. Some studies suggest the association between rewarding center and control of food intake [16]. It is suggested that intake of large amount of drug or food can unbalanced these circuits and result in compulsive usage of food or drugs. Thus proper function of these circuits can result in balanced intake and food and drug intake has been related to close circuits. These circuits are also regulated by endogenous opioids [17]. Also enough neurogenesis dependent on establishment of proper feeding habit, and enough neurogenesis helps habits that is needed for successful tolerance of morphine addiction. Excessive feeding can be addictive behavior that is the result of disturbances of reward center circuits [18]. So changes in feeding behavior can be considered as a sign of proper rewarding center function and neurogenesis regulates this circuit [19,20]. So in this study feeding behavior was assessed to examine the effect of morphine and socialization on feeding center that itself is regulated by neurogenesis.

Feeding behaviors are well regulated behaviors for obtaining and consuming foods. These ingestive behaviors are regulated by neural circuits embedded within central nervous system [21]. However, current literature lacks exacts mechanisms involved in the regulation of feeding behavior. Classical studies have indicated the role paraventricular nucleus and lateral hypothalamic area as feeding centers. In addition, arcuate hypothalamic nucleus has recently gained much attention for the neuronal control of appetite and metabolism [14]. Interestingly, hippocampus has been recently highlighted for regulation of food intake [15,22]. Kanoski et al. [8] showed that ghrelin signalling in ventral subregion of hippocampus contributes to food intake and learned appetite behaviors.

Regulation of food intake also relies on communication between hypothalamic homeostatic circuits and reward circuits [16]. It is suggested that intake of large quantities of food/drug can disturb these circuits and may result in compulsive ingesting behaviors. In addition, endogenous opioids are also involved in the regulation of food intake and it appears to be linked with reward-dependent feeding [17].

Relapse to drug abuse can happen through two major mechanisms: 1) inadequacy of rewarding center that manifest itself through repeated and compulsive abuse despite adverse effects 2) co morbid psychiatric disorders occurrence such as anxiety and depression [23]. Neurogenesis reduces side-effects of drug abuse through its ability to positively enhance function of rewarding center [24] and also through improvement of co morbid psychiatric disorder such as depression and anxiety [25,26]. In this regard feeding behavior can also be regulated by rewarding center in a positive manner [27]. A disturbance of feeding behavior through increase in intake of food is the result of disturbed rewarding center function.

Transition from occasional usage to uncontrolled and compulsive state is not a predictable behavior [28]. Defining behaviors that render development of such behavior is important. In this study, feeding behavior was assessed as an indicator of good prognosis. Since normal feeding behavior is indicative of healthy functioning of rewarding center. Also proper feeding is associated with behaviors that prevent addiction development [18]. In addition, addiction involves pathological disruption of neural processes that are normally important for reward-related learning and memory. For successful drug withdrawal and abstinence, intact short-term memory is essential [29]. Thus, disturbed feeding patterns can be considered as co-morbid with memory impairment and mood imbalances that worsen prognosis in addiction period.

Zinc is an essential element for many types of enzymes in brain [30]. Of the organs in brain that needs zinc is hippocampus that is involved in memory and other cognitive abilities. In rats with Alzheimer disease, zinc deficiency deteriorates cognitive function [31]. Neurogenesis can be affected by alternations of zinc level and bioavailability [31,32].

The aim of this study is to prove the hypothesis that socialization in addiction period increases neurogenesis that in turn increases food intake as an indicator of proper rewarding center function and also improves co morbid psychiatric disorder such as mood disturbance and short term memory that causes relapse to drug abuse.

2. MATERIALS AND METHODS

2.1 Animal Care

The experimental protocols followed in this study were conformed to the guidelines for the care and use of laboratory animals published by national institution of health (NIH Publication No. 85-23, revised 1996) and was further approved by the institutional ethical committee at Tehran University of medical science (Tehran, Iran).

2.2 Animals

In this study male Sprague-Dawley rats weighting 200-250 grams were used. In each group 8 rats were used in four groups. It should be noted that one rat was used for modeling socialization in two socialized groups. So overall, 48 rats were used (Fig. 1).

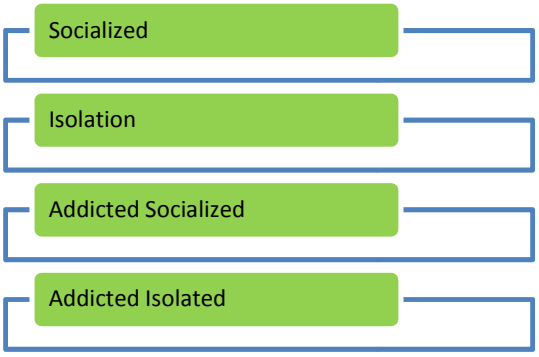


Fig. 1. Experimental groups

2.3 Addiction

Rat's receives 0.75 mg/rat/day morphine sulphate (IP) for 14 days. Morphine was prepared in powder form (Temad Co.). It was dissolved in distilled water.

2.4 BrdU Preparation

BrdU is analogue of base thymidine that is incorporated into the DNA of newly generated neurons that is divided in dentate gyrus of hippocampus. After immunostaining the neurons that contain BrdU get color of brown. BrdU powder was purchased from Sigma-Aldrich

Company. 50 mg/kg/rat were dissolved in normal saline (N/S 0.9%). Then it was injected interaperitoneally once a day at the same time.

2.5 Isolation

Animals were isolated in cages covered with black plastic for 14 days plus one week for adaptation to environment.

2.6 Socialization

Two animals were kept together in one large cage.

2.7 Experimental Procedure

After addiction period in day 14 Y-maze, feeding behavior and blood sugar were assessed. For performing novelty a suppressed feeding test rat for 24 hour fasted and in the following day experiment was done. Then rats anesthetized and brain was perfused with paraformaldehyde 4%. Then the brain removed from the skull for obtaining brain sections for immunohistochemistry (Figs. 2 and 3).

2.8 Feeding Behavior Assessment

Twenty-four hour food and water intake were noted in rats. Food and water were weighed in the beginning and compared with that at the end. For this experiment, all rats were housed separately and tap water and food pellets were introduced to each cage.

2.9 Novelty Suppressed Feeding Test

This test was performed to assess anxiety-induced hypophagia in rats. Rats were housed individually, and food pellets were removed from their cages. Water was made freely available. After 24 hours, rats were tested. The testing apparatus consisted of a square open field chamber (30 cm long × 30 cm wide × 20 cm high). A piece of chow was placed in the center of the testing apparatus. Each rat was placed in a corner of the testing apparatus, and the latency to the first feeding episode was recorded for 5 min [33].

2.10 Y-maze

We used a Y-shaped maze with three arms placed at 120° angle from each other. Each arm was 40 cm long, 30 cm high and 15 cm wide converging on a triangular central area with 15 cm at its longest axis. This test was used to assess short term memory involving many parts of brain like; hippocampus, basal forebrain, septum and prefrontal cortex. In this study we considered prefrontal cortex function for short term memory assessment by recording spontaneous alternation in a single 8 minute session. Each rat was placed at one end of the maze and then allowed to move freely.

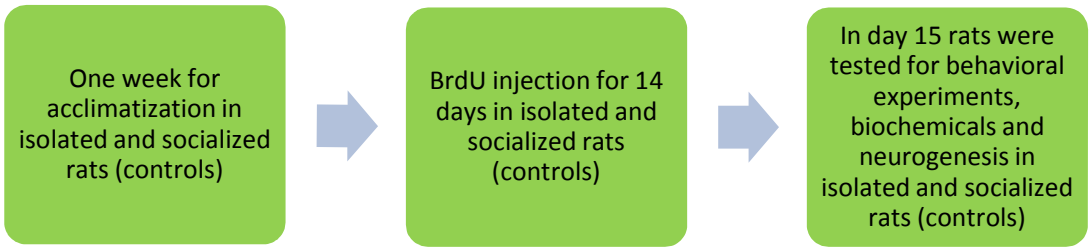


Fig. 2. Interventions in control groups

Fig. 3. Interventions in treatments groups

The sequence of each arm entry recorded manually (i.e., ABCBCAACACBABCB, etc.). A spontaneous alternation behavior, which is regarded as a measure of spatial memory, was defined as the entry into all three arms on consecutive choices in overlapping triplet sets (i.e., ABC, ABA, CAB, and CBC). The percent spontaneous alternation behavior was calculated as the ratio of actual to possible alternations. Percent Alternation = Actual Alternation (i.e., ABC, CBA = 6) / Maximal Alternation*(i.e., ABCBCABCABCACBA = 15 – 2 = 13) ×100 = (6/13)×100 = 46.15%. * Total number of arms entered minus 2. The test was done once for each animal [34].

2.11 Blood Sugar

For performing this experiment tails of rats were cut with scissor for obtaining blood. Blood was placed in glucose strips test. Then glucose level was assessed with glucometer (Roche, No.GN02531992).

2.12 Zinc Assessment

For obtaining plasma, after thoracotomy before paraformaldehyde perfusion five milliliter blood was taken from left heart. After coagulation and centrifugation plasma was collected in microtubes and stored in -70 centigrade. For preparing plasma for analysis of zinc level first they were incubated with 65% citric acid for 2 hours. Then for one hour they were incubated with 65% perchloric acid. The final solution was examined with atomic spectroscopy (Varian-220-FS-aa). After obtaining absorbed wavelength it was adjusted with calibration curve and expressed as p.p.m.

2.13 Neurogenesis

For preparation of brains for BrdU staining, BrdU was injected 14 days interaperitoneally. It should be noted that in acclimatization period BrdU was not injected. BrdU is an analogue of thymine base which is incorporated in DNA of newly proliferated neurons in dentate gyrus of hippocampus. However, after day 14 rats before sacrificing, rats were sedated with xylazine (10 mg/kg) and anesthetized with ketamine (100 mg/kg). Brain after fixation with paraformaldehyde was removed from the skull and for one week kept in mixture solutions of paraformaldehyde and sucrose. Brain sections in region of dentate gyrus of hippocampus were prepared with cryostat with the thickness of 30 µm. Brain sections were stained according to kit protocol with primary and secondary antibody (5-Bromo-2′-dU Labeling and Detection Kit II; Roche, Germany, Cat. No. 11299964001-en-17).

2.14 Quantification of BrdU Positive Cells

Every fifth section throughout the hippocampus (total 10 sections for each rat) was processed for BrdU immunohistochemistry. All BrdU-positive cells in the sub granular zone (SGZ), hilus, granular cell layer (GCL) and molecular layer were assessed using light microscope (Zeiss, Germany) were counted in a blinded manner bilaterally. BrdU positive cells were counted in dentate gyrus in rostrocaudal fashion. As shown in Fig. 10 regions that were counted in hippocampus were whole dentate gyrus. BrdU positive neurons appeared much bigger than usual and appeared as singles or cluster cells. Mean were estimated for every five sections in this study and neurons were not multiplied by each section count [13].

2.15 Statistics

Data analysis was performed with SPSS version 22 and Graph Pad prism version 5. Univariate (Two-way) ANOVA was performed with two factors (Addition × Socialization) and if variance was significantly different, Post hoc Tukey was done for analysis of mean difference. Data was represented as mean ± SEM. * means significant difference between adjacent group and $, & and # means significant different between those apart from each other.

3. RESULTS

3.1 Short Term Memory

Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for short term memory (F: 17.993, DF: 1 and P: 0.008). Post hoc analysis with Tukey showed, in addiction period, short term memory was impaired in addicted isolated rats compared to addicted socialized rats in addiction period (Interaction between factors (Socialization × Addiction) F: 17.993, DF: 1 and P: 0.008) (Fig. 4).

3.2 Feeding Behavior

A. Statistical analysis with Univariate (Two-way) ANOVA showed that variance is

significantly different among four groups for food intake (F: 26.544, DF: 1 and P: 0.000). Post hoc analysis with Tukey showed, In addiction period, total amount of food and water in 24 hour decreased in addicted isolated rats compared to addicted socialized rats (Interaction between factors (Socialization × Addiction) F: 8.375, DF: 1 and P: 0.011). Also rats in isolation group consume less food than socialized group (P: 0.000).

B. Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for water intake (F: 7.803, DF: 1 and P: 0.011). Post hoc analysis with Tukey showed, Addicted isolated rats consume more water than addicted socialized rats that may indicator of high metabolism and more toxic substance (Interaction between factors (Socialization × Addiction) F: 7.479, DF: 1 and P: 0.013). Adversely rats in isolation group consume less water than socialized rats that is indicator of fewer metabolisms in this group (P: 0.046) (Figs. 5A and B).

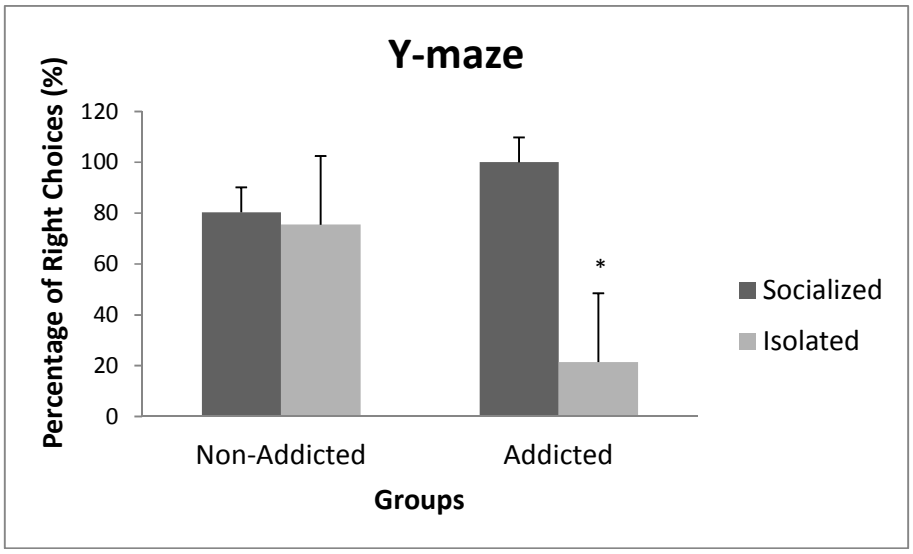
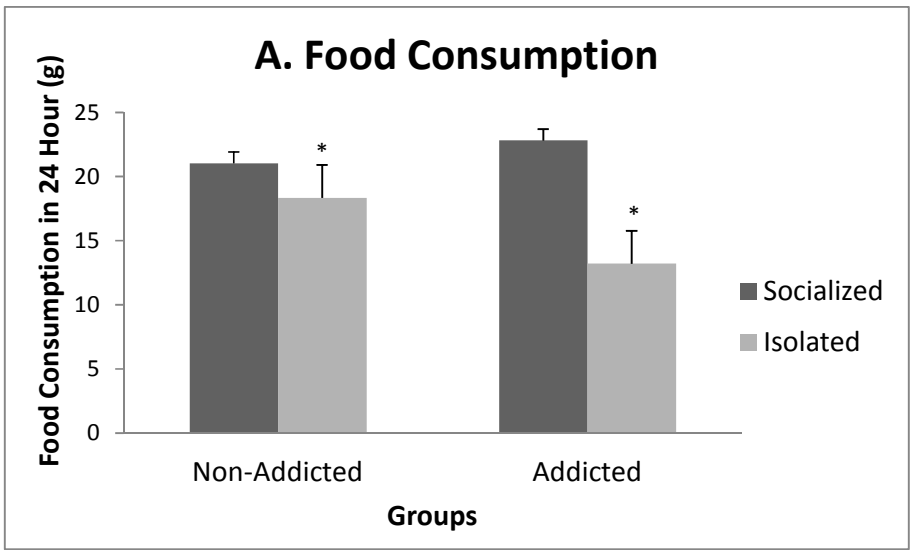


Fig. 4. Short term memory was assessed by Y-maze / sec (n=8)

Data was represented by Mean ± SEM. means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups)*



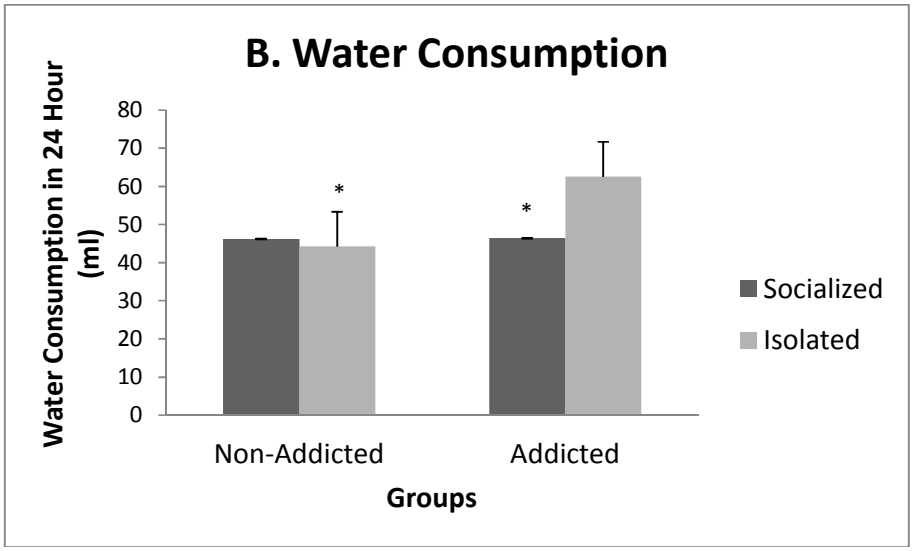


Fig. 5. A. Amount of food intake / gram (n=8) B. Amount of water intake / ml (n=8)
Data was represented by Mean ± SEM. ⋆ means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups)

3.3 Blood Sugar

Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for blood glucose (F: 13.940, DF: 1 and P: 0.001). Post hoc analysis with Tukey showed, in addiction period, level of glucose was increased in addicted isolated rats compared to addicted socialized rats (Interaction between factors (Socialization × Addiction) F: 4.763, DF: 1 and P: 0.041). Also isolated rats had higher level of glucose than socialized group P: 0.0393) (Fig. 6).

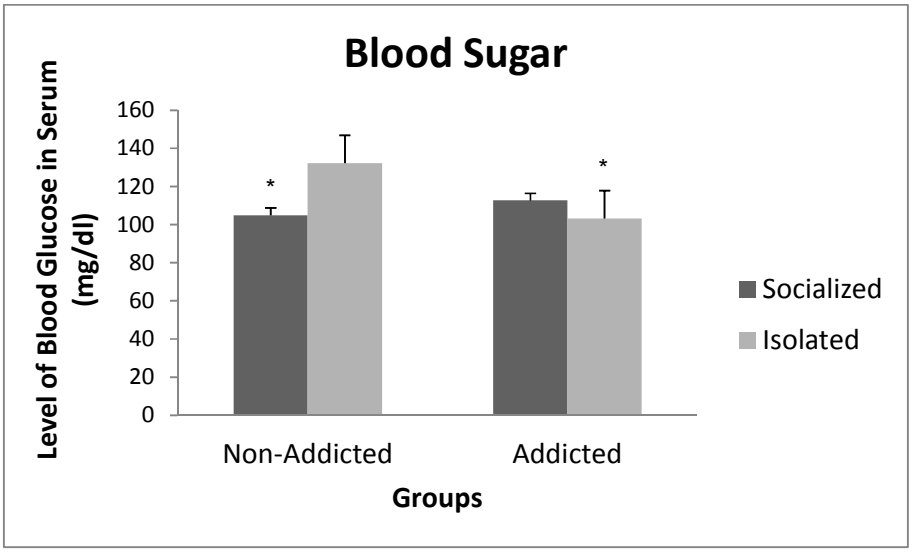


Fig. 6. Level of blood glucose mg/dl (n=8)
Data was represented by Mean ± SEM. ⋆ means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups)

3.4 Anxiety Level Assessing with Novelty Suppressed Feeding (NSF) Test

Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for anxiety level assessing with NSF (F: 7.724, DF: 1 and P: 0.032). Post hoc analysis with Tukey showed, in addiction period, level of anxiety was increased in addicted isolated rats compared to addicted socialized rats (Interaction between factors (Socialization × Addiction) F: 9.553, DF: 1 and P: 0.005). Isolated rats had lower anxiety level compared to socialized rats in control groups (P: 0.026). Also Addicted isolated rats had higher anxiety compared to isolated rats (P: 0.0062) (Fig. 7).

3.5 Zinc Assessment

Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for zinc level in serum (F: 50.541, DF: 1 and P: 0.000). Post hoc analysis with Tukey showed, in addiction period, in addicted socialized rats zinc increased compared to addicted isolated rats (Interaction between factors (Socialization × Addiction) F: 25.925, DF: 1 and P: 0.001). In isolated rats zinc decreased compared to socialized rats in control groups (P: 0.045). Also, in addicted socialized rats zinc increased significantly compared to control and isolated rats (P: 0.045) (Fig. 8).

3.6 Neurogenesis

Statistical analysis with Univariate (Two-way) ANOVA showed that variance is significantly different among four groups for newly generated neurons (F: 13.804, DF: 1 and P: 0.002). Post hoc analysis with Tukey showed, neurogenesis decreased in addicted isolated rats compared to addicted socialized rats during addiction period (Interaction between factors (Socialization × Addiction) F: 5.648, DF: 1 and P: 0.030). Socialized rats in control groups had more neurogenesis than rats in isolation (P; 0.000). Addicted socialized rats had fewer neurogenesis than socialized rats (0.02). Rats in isolated group had more neurogenesis than addicted isolated rats (P: 0.000) (Figs. 9 and 10).

4. DISCUSSION

For the first time, our study shows that socialization during addiction period improves feeding behavior, neurogenesis, mood disturbances and stress responses. Furthermore, we showed that addiction groups have worse prognosis than socialized and isolated groups.

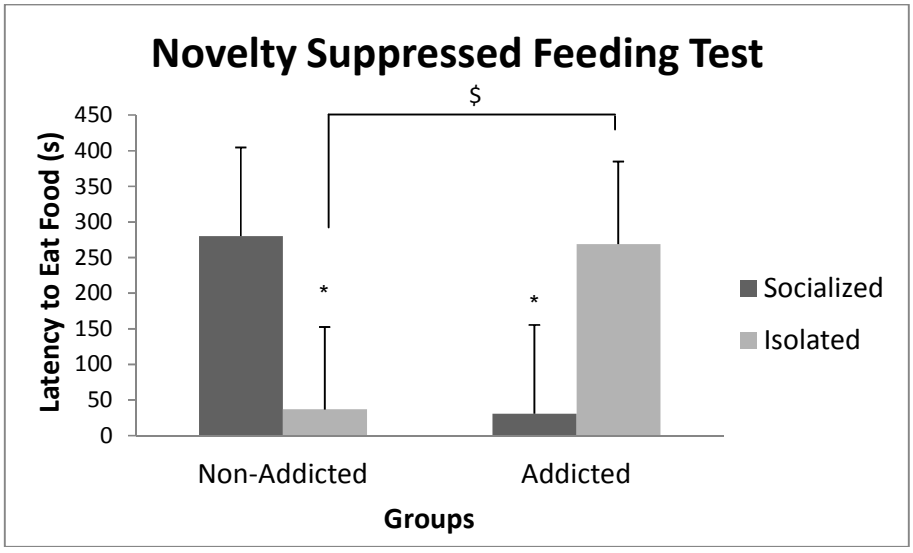


Fig. 7. Level of anxiety / sec (n=8)

*Data was represented by Mean ± SEM. * means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups) and $ between those apart from each other*

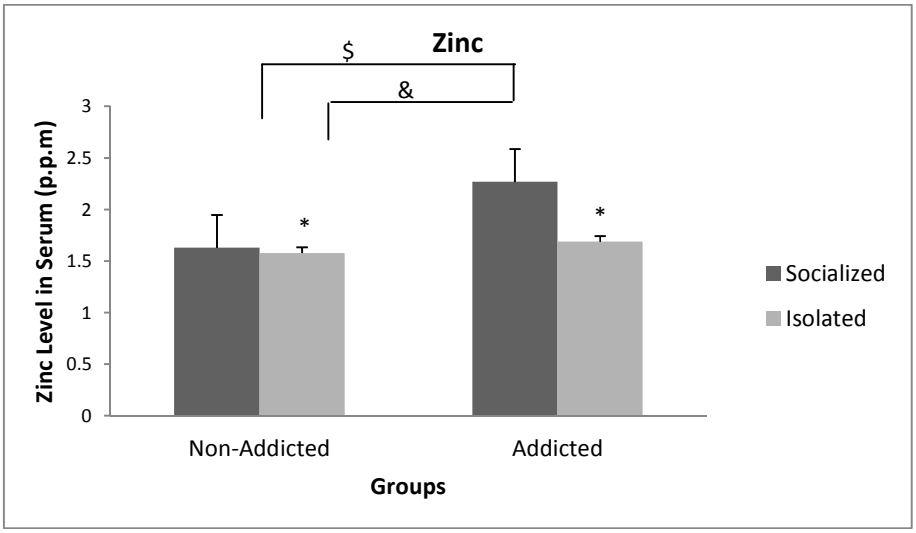


Fig. 8. Level zinc in serum assessed by atomic spectrophotometer (n=6)

*Data is represented as mean ± SEM. * means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups) and $ and & between those apart from each other*

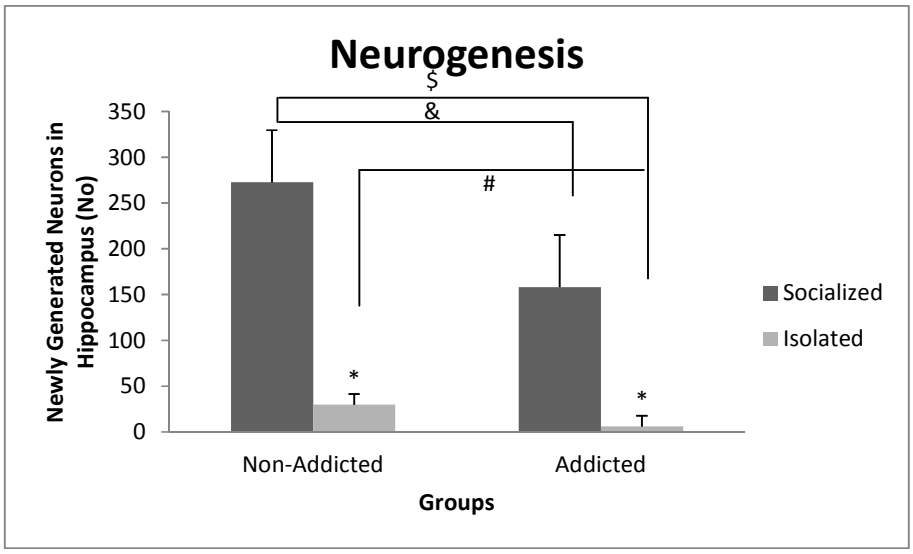


Fig. 9. Neurogenesis in dentate gyrus of hippocampus (n=6)

*Data was represented by Mean ± SEM. * means significant difference between adjacent groups (Socialized × Isolated in Non-Addicted groups and Socialized × Isolated in Addicted groups) and $, # and & between those apart from each other*

Satiety - the absence of hunger or feeling of fullness is regulated in several ways. Previous studies have revealed its time dependent regulation. Forty-eight hour food deprivation elicited some responses in different from those in short-term (24 h and 6 h) food deprivation [21]. In this study, we observed that hippocampal neurogenesis affects short-term food deprivation [35]. It has been suggested that BDNF plays an important role in regulating hippocampal neurogenesis and it may affect neuronal circuits involved in satiety [36]. In addition, neuropeptide Y - a neurotransmitter involved in neurogenesis and neuronal guidance, also controls food intake [15]. Also in the other way it can alter food intake by changing emotional states that impart regulated by hippocampus. In this study it was assessed by novelty suppressed feeding test.

Emotional states can alter feeding behaviors by hormonal influences [37]. Hormones like glucocorticoids, leptin, adiponectin, resistin, and insulin affect hippocampal neurogenesis and this in return may influence the function of feeding center [38]. Furthermore, depressed state can motivate an individual to take high-fat diet which can reduce hippocampal neurogenesis [39].

Adult hippocampal neurogenesis is highly influenced by isolation-induced stress [40]. Previously, stress has been studied in two forms: acute and chronic. The effect of acute stress on neurogenesis is quite controversial. It has been shown that acute stress may enhance hippocampal neurogenesis via secreted astrocyte fibroblast growth factor -2 (FGF-2).

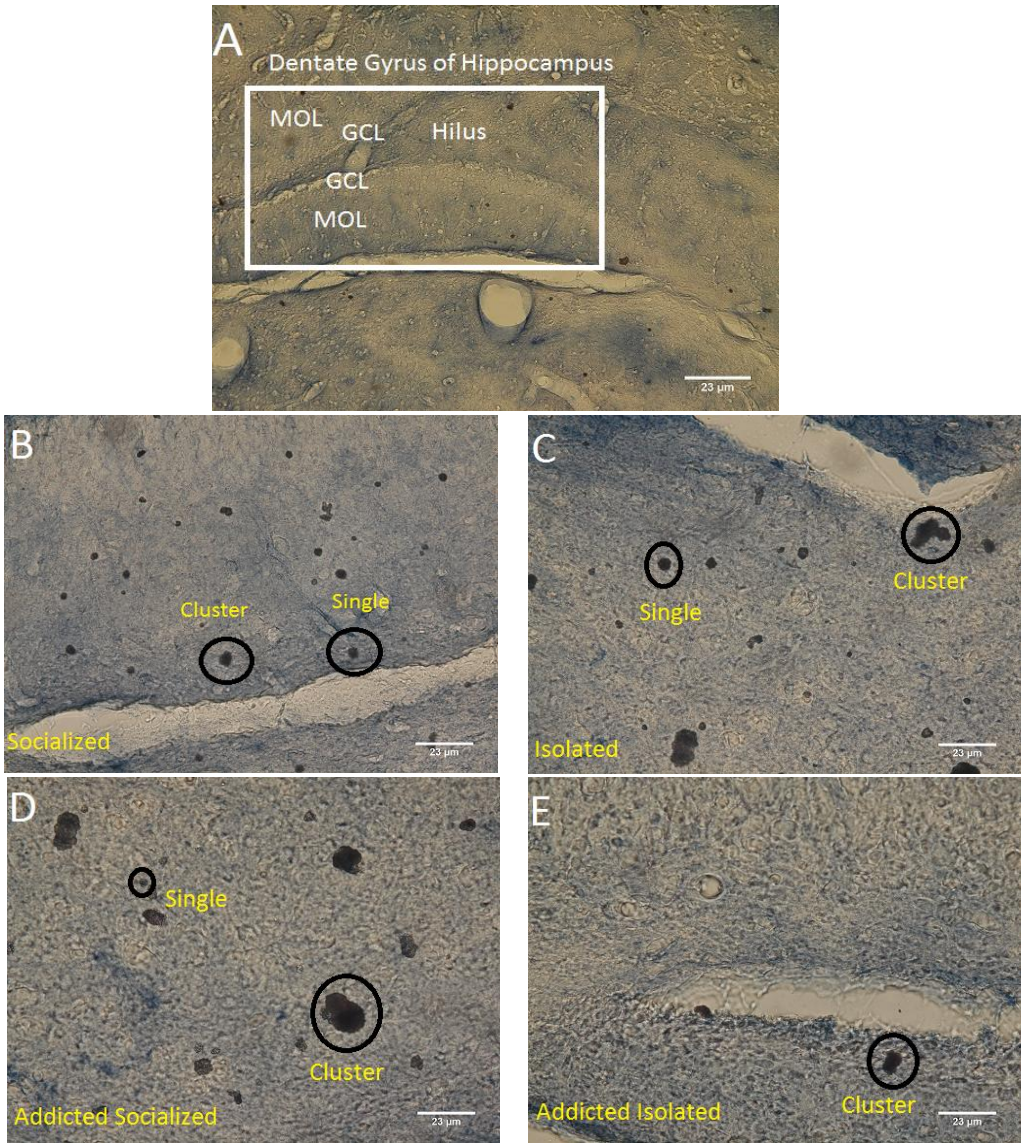


Fig. 10. A) Different parts of dentate gyrus of Hippocampus have been marked in picture Counting of BrdU positive cell has been done in these areas. It has three parts: molecular layer (MOL) (outer (OML), middle (MML) and inner (IML)), granular cell layer (GCL) and hilus (sub granular zone (SGZ) and deep hilus). Newly generated neurons were counted in these areas (40X magnification). B, C, D and E) BrdU positive cells have been colored brown in all four groups. They may be in single or cluster forms. It should be noted that all newly generated neurons have not been marked by arrows (400X magnification) (n=6)

Data was represented by Mean ± SEM

On the other hand, studies indicate that social defeat and restraint stress can reduce the rate of neurogenesis [41-43], but prolonged restraint stress may not affect it [44-46]. Therefore, it seems that duration, frequency and intensity of stressors may influence neurogenesis.

It is well evident that chronic stress decreases hippocampal neurogenesis, especially in neonatal mice [47]. It may reduce survival and inhibit proliferation of new neurons [48]. Interestingly, hippocampus - dependent learning as demonstrated by water maze training, causes acute downregulation of adult neurogenesis [49]. In accordance to previous studies, we found that social isolation - induced chronic stress reduces neurogenesis during drug addiction period.

Stressful events lead to the activation of hypothalamus-pituitary-adrenal (HPA), which in turn, triggers glucocorticoid release. It has been observed that administration of corticosterone decreases both, proliferation and survival of new neurons [50]. Furthermore, elevated pro-inflammatory cytokines have also been linked to neurodegeneration [51,52]. Following stress, IL-1 expression has shown to be dramatically enhanced in hypothalamus [53,54].

Adult hippocampal neurogenesis is vital for the regulation of feeding behavior and neuropeptide Y can potentiate both, neurogenesis and food intake. Hokfelt et al. [15] showed that mice deficient in Y_1 or Y_2 receptor had fewer proliferating precursor cells and neuroblasts in SVZ and rostral migratory stream and fewer neurons in the olfactory bulb expressing calbindin, calretinin or tyrosine hydroxylase. We found that socialization promotes food and water intake during addiction period, thereby attaining the state of nutritional balance.

Another important subject to be discussed is the role of circadian rhythm in regulating neurogenesis and feeding behavior [55]. Furthermore, feeding behavior is affected by light- dark cycle. In a complex circadian control pathway, light-controlled rhythms are primary regulators of neuronal proliferation, and hormonal and activity-driven influences over neurogenesis are secondary events [55]. In a study, glucocorticoids have shown to increase food intake in rats by increasing sensitivity to leptin and insulin [56]. In addition to increased sensitivity to leptin and insulin, glucocorticoids also increase the sensitivity to melanocortin action [57]. Hence, in our study, reduced appetite can be partly attributed to changes in circadian rhythm and hormonal sensitivity caused by isolation.

Current literature lacks much information about the effect of diet and nutrition on adult hippocampal neurogenesis. In a study, high-fat diet impairs hippocampal neurogenesis in male rats [58]. However, other diets have not been studied yet. Neuronal lipoprotein lipase (LPL) is essential for regulating energy balance by hydrolyzing triglycerides. Picard et al. [59] demonstrated that inhibition of hippocampal LPL activity can increase ceramide (a core constituent of all complex sphingolipids) biosynthesis, which in turn enhances neurogenesis. It is evident that ceramide levels control dendritic spine maturation and cognition. Furthermore, caloric restriction and exercise enhances progenitor cell survival and proliferation, respectively [58,60], and social isolation can delay this exercise-induced neurogenesis [61]. The responding ability of new hippocampal neurons to triglycerides changes shows that new neurons may be affected by nutritional status affect [59]. Furthermore, Perera et al. [36] reported that higher blood glucose levels were associated with higher rate of neurogenesis. The current study establishes that socialization can improve feeding behavior and therefore, can attain nutritional balance in the body. However, further studies are needed to assess effects of different types of diet on neurogenesis.

Specific mechanisms that link hippocampal neurogenesis with the hypothalamus and appetite regulation remain unclear. There are two reasons for considering the involvement of hippocampus in regulating energy balance. First, hippocampus is part of limbic system and appetite center is located in hypothalamus. Secondly, hippocampal projections spread to adjacent areas like feeding center [36]. In addition, a study shows that BDNF knock-out rats have poor regulation of food intake and demonstrate diminished hippocampal neurogenesis [36,62]. We observed low glucose intake by isolated rats during addiction, which can be due to the increase in metabolic demand for restoring neurogenesis.

Leptin- an adipose derived hormone, effects hypothalamic receptors that control food intake. It increases hippocampal cell proliferation by interacting with leptin receptors on hippocampal progenitor cells [36,63].

Ghrelin is a hormone and neuropeptide which is involved in regulating energy balance via hypothalamic circuits [64]. Ghrelin also plays an important role in regulating reward perception in dopamine neurons that link ventral tegmental area to nucleus accumbens [65]. However, the role of exogenous Ghrelin in promoting neurogenesis via regulating behavior needs to be investigated.

Independent of its cognitive functions, hippocampus plays a distinctive role in mediating mood balance. Current literature demonstrates that selective impairment of hippocampal neurogenesis can exhibit a striking increase in anxiety-related behaviors [5,66]. Hippocampus may respond to stress by altering nutritional balance in order to combat adverse effects of mood disturbance. Effect of stress on feeding behavior is controversial. According to some studies, stress increases food intake, whereas other reports contradict this observation. However, sustained chronic stress seems to decrease appetite [67].

Social interaction profoundly effects neurogenesis and this effect can at least be partly attributed to oxytocin [68]. A study suggests the therapeutic effect of oxytocin for treating amphetamine abuse [69].

In this study zinc decreased in isolated rats, also addicted socialized rats had higher level of zinc compared to isolated and control rats. This emphasizes on role of pair state (socialization) on balance of zinc level. Zinc is a necessary element may be for enough level of neurogenesis [32]. Also neurogenesis in hippocampus may directly or indirectly through rewarding center regulates addictive behaviors. Changes in neurogenesis can be resulted in some ways by reduced level of zinc such as lower level of connective tissue that result in lower level of stem cells niches [31].

5. CONCLUSION

Hippocampal neurogenesis regulates feeding behavior along with co morbid psychiatric disorders in a positive manner. These positive effects increase with socialization. With increasing neurogenesis with socialization, rewarding center function back to normal state sooner. So with restoring neurogenesis adverse effect of drug abuse can be prevented. Also this study showed that there is interrelated relationship between feeding behavior and co morbid psychiatric disorders such as depression and anxiety in addiction period and both are regulated by neurogenesis.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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