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Role of Hippocampal Neurogenesis in Regulation of Feeding Behavior during Withdrawal Period in Socialized and Isolated Rats

Hamidreza Famitafreshi[1], Morteza Karimian[2*] and Sulail Fatima[1]

[1]Department of Physiology, Tehran University of Medical Sciences - International Campus, Tehran, Iran.
[2]Tehran University of Medical Sciences, Tehran, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Author HF with the help of author MK designed the study and wrote the protocol. Author HF performed the experiments, managed the literature searches and wrote the first draft of the manuscript with the help of author MK. Author SF rewrote the final draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Introduction: Hippocampal neurogenesis is essential for cognitive functions like memory and learning. However, other functions of hippocampus are not well understood. We aimed to study the role of hippocampus in regulation of feeding behavior during withdrawal period.
Materials and Methods: Forty eight male Sprague-Dawley rats were randomly divided into four experimental groups: socialized, isolated, withdrawal isolated group and withdrawal socialized group. At the end of study, short - term memory, feeding behavior, blood glucose levels, corticosterone, copper, anxiety and neurogenesis were assessed.

**Corresponding author: E-mail: karimian@tums.ac.ir;*

Results: Socialization during withdrawal, increased food intake in rats. In isolated rats, short term memory was significantly impaired and neurogenesis was reduced. Blood glucose and anxiety levels were found to be higher in isolated rats. Socialization reduced corticosterone level and copper in serum in rats.
Conclusion: Socialization improves hippocampal neurogenesis which in turn regulates feeding behavior. Feeding behavior imparts regulated by hippocampus directly and also indirectly by co morbid psychiatric disorder.

Keywords: Neurogenesis; Y-maze; feeding; corticosterone; novelty suppressed feeding test; withdrawal; copper and glucose.

1. INTRODUCTION

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

Socialization promotes new habits and skills. Social interaction is especially important during childhood as it facilitates learning, reasoning, comprehension and critical thinking. In adults, 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 [5]. In contrast, social isolation during adulthood can bring about a variety of troubles like personality disorder, family instability and social problems [6]. Social isolation impairs learning and memory formation, and promotes mood disturbances [7].

Feeding behaviors are well regulated. These ingestive behaviors are regulated by neural circuits embedded within central nervous system. 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 [8]. The hippocampus has been recently highlighted for regulation of food intake [9,10]. Kanoski et. al showed that ghrelin signalling in ventral subregion of hippocampus contributes to food intake and learned appetite behaviors [4]. Regulation of food intake also relies on communication between hypothalamic homeostatic circuits and reward circuits [11]. It is possible 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 [12].

Abstinence from drug of abuse is often not successful and drug relapse remains a major problem. Understanding the pathophysiological basis of drug relapse can aid in successful drug withdrawal. Transition from occasional usage to uncontrolled and compulsive state is not a predictable behavior. Being able to delineate the development of such behaviors is important. In this study, feeding behavior is assessed to determine if it is associated with good prognosis. Since normal feeding behavior is indicative of healthy functioning of rewarding center, proper feeding for developing addiction. 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 [13]. Thus, disturbed feeding patterns co-morbid with memory impairment and mood imbalances can be indicative of bad prognosis during withdrawal period.

Elevated corticosterone level is a marker of relapse to drug abuse and poor stress response [14]. The elevation of corticosterone is associated with elevated corticotrophin-releasing factor (CRF) which plays an important role in stress-induced drug relapse. Pharmacological blockade of CRF system has shown to inhibit drug-seeking and drug-taking behaviors [15,16].

Copper (Cu) is an element essential for cellular function and it acts as a cofactor for many enzymes involved in biochemical reactions. In the nervous system, Cu ions take part in neurotransmitter metabolism and synaptic activity. Using x-ray fluorescence microscopy, it has been observed that subventricular contains a very high Cu concentration as compared to other brain areas [17]. Thus, it can be speculated that Cu may be involved in neuronal proliferation and differentiation associated with the subventricular zone.

In this study, we hypothesize that socialization during withdrawal period facilitates the reward center for the maintenance of positive behaviors such as feeding and prevents anxiety. Furthermore, we explored the role of hippocampal neurogenesis in the regulation of feeding behavior.

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 Institutes of Health (NIH Publication No.85-23, revised 1996) and were further approved by the institutional ethical committee at Tehran University of Medical Sciences (Tehran, Iran). Forty eight male Sprague-Dawley rats (weighing 200 to 250 g) were housed in an air-conditioned colony room maintained at 21–23℃ with 12 hours light-dark cycle. All animals had with free access to food and water. The animals were divided into 4 groups (n=8); socialized (control), isolated (control), withdrawal isolated and withdrawal socialized group. Sixteen rats just were used for modeling socialization without any other intervention (Fig. 1).

2.2 Isolation and Socialization of Rats

Rats in the isolated group were housed individually in cages with walls covered with black plastic. Isolated rats were housed in separate rooms in order to attain true isolation. The rooms were well-ventilated and kept quiet. In socialized group, rats were housed in pairs and the cages left transparent. Rats were caged for 1-week adaptation period followed by two weeks of experimental period (Fig. 2).

2.3 Addiction and Withdrawal

For adaptation, all rats received 0.75 mg/day/i.p. of morphine sulphate for three days. Rats were rendered morphine dependent by interaperitoneally infusions of increasing doses of morphine (from baseline dose: 5mg/kg/1st day to final dose: 35/mg/kg/7th day) for 7 days twice a day. Next, Naltrexone was injected (3 mg/kg/i.p) in day 8. Drug doses were selected from preliminary study performed at our laboratory (unpublished data) and other previous studies [18, 19]. Naltrexone was used for preparing rats for better tolerance of withdrawal period (Fig. 3).

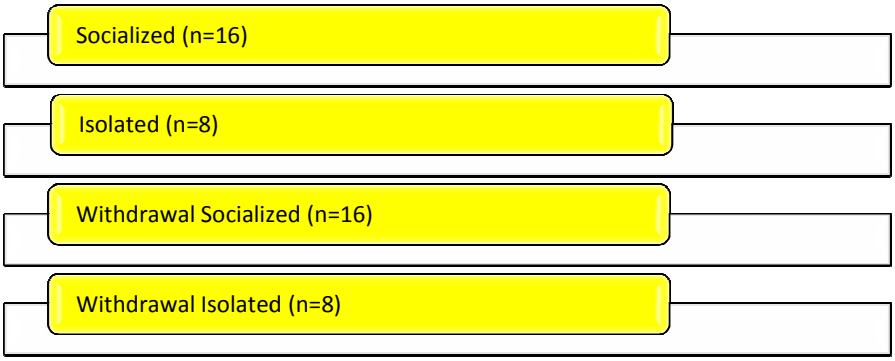


Fig. 1. Experimental groups

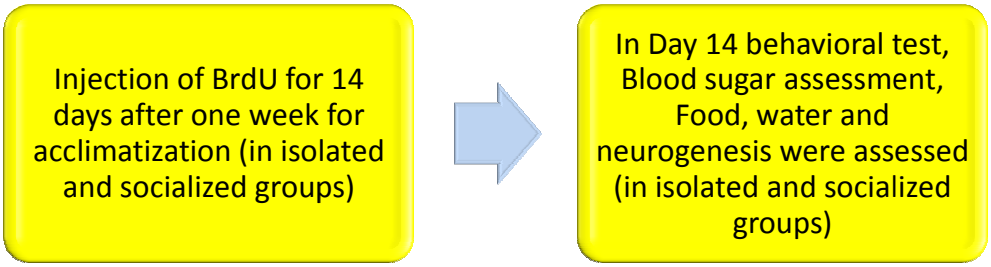


Fig. 2. Interventions in control groups

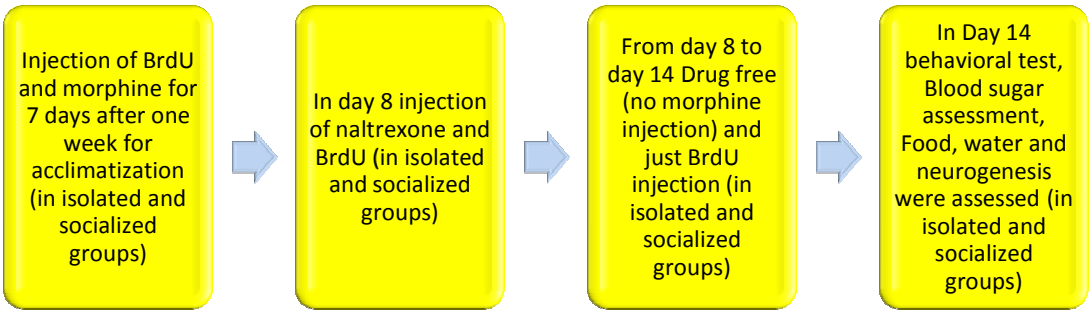


Fig. 3. Interventions in treatment groups

2.4 BrdU Preparation

BrdU is analogue of base thymidine that incorporates into the DNA of newly generated neurons and gives brown stain to them. BrdU powder was purchased from Sigma-Aldrich Company and 50 mg/kg/rat was dissolved in normal saline (N/S 0.9%). BrdU was injected intraperitoneally once a day for 14 days.

2.5 Experimental Design

At the end of 14th day, spatial memory (using Y-maze), feeding behavior and blood sugar levels were assessed. Furthermore, novelty suppressed feeding test (NSF) was performed. Rats were anesthetized and blood was collected and brains were perfused with paraformaldehyde 4%. The rats were decapitated and their brains were sectioned to study neurogenesis by counting BrdU positive cells.

2.6 Assessment of Feeding Behavior

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.

2.7 Novelty Suppressed Feeding Test (NSF)

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 [20].

2.8 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. The sequence of each arm entry was 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 rat [21].

2.9 Blood sugar levels

Blood was obtained from the tail vein of the animal. Next, blood was put over the strip and glucose level was assessed using glucometer (Roche, No.GN02531992).

2.10 Assessment of Corticosterone

Animals were anesthetized for collection of blood samples from heart. Serum corticosterone levels were assessed using ELISA kit (Sigma Aldrich).

2.11 Plasma Copper Level

Following thoracotomy, 5ml blood was obtained from heart and centrifuged. Plasma was collected and stored in microtube at -70^{0}C. For measuring copper levels, plasma was incubated with 65% citric acid for 2hr and 65% perchloric acid for 1hr. Next, the absorbance was obtained using atomic spectroscopy (Varian-220-FS-aa) and was adjusted according to calibration curve Plasma copper levels were expressed as p.p.m.

2.12 Neurogenesis

At the end of 14th day, rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg). After thoracotomy, all rats were first perfused with normal saline and then, with paraformaldehyde 4% via intracranial infusion. After fixation, the brains were removed from the skull. For the first 2 days, the brains were kept in PBS + paraformaldehyde 4% and then at day 3, in sucrose 10% + paraformaldehyde 4% + PBS. Throughout day 4, the brains were kept in sucrose 20% + paraformaldehyde 4% + PBS and for the rest of the days they were kept in sucrose 30% + paraformaldehyde 4% + PBS. The cryosections (30 µm) were prepared from dentate gyrus of the hippocampal region. Immunohistochemistry was performed for ten sections from each brain, five of which were stained for BrdU positive neurons with anti-BrdU antibody kit (5-Bromo-2′-dU Labelling and Detection Kit II; Roche, Germany, Cat. No. 11299964001-en-17). BrdU-positive cells in dentate gyrus were counted under light microscope [7].

2.13 Statistics

Data were analyzed using SPSS version 22 and Graphpad prism 5. Uni-variate (Two-way) ANOVA followed by Pos-hoc Tukey was performed with two factors (withdrawal × socialization). Data were represented as mean ± SEM and $P<0.05$ was considered significant.

3. RESULTS

3.1 Short Term Memory Assessed with Y-maze

During withdrawal, short term memory was markedly impaired in isolated rats as compared to socialized rats. Also isolated rats had better short memory than withdrawal isolated rats (Fig. 4).

3.2 Feeding Behavior

During withdrawal, isolated rats consumed significantly lesser food and water as compared to socialized rats. In addition, isolated rats consume more food and water than withdrawal isolated rats (Fig. 5A and B).

3.3 Blood Sugar Level

During withdrawal, isolated rats had higher blood glucose level as compared to socialized rats. Also isolated rats had higher blood glucose level than withdrawal isolated rats (Fig. 6).

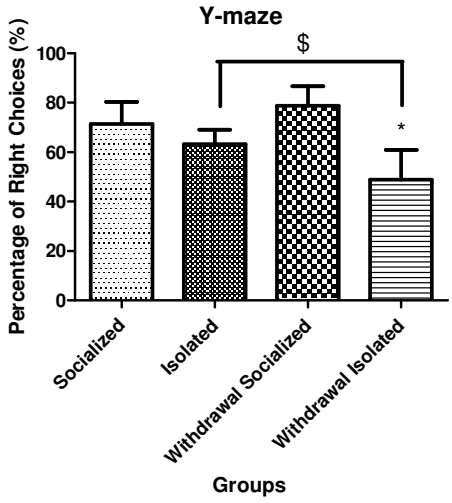


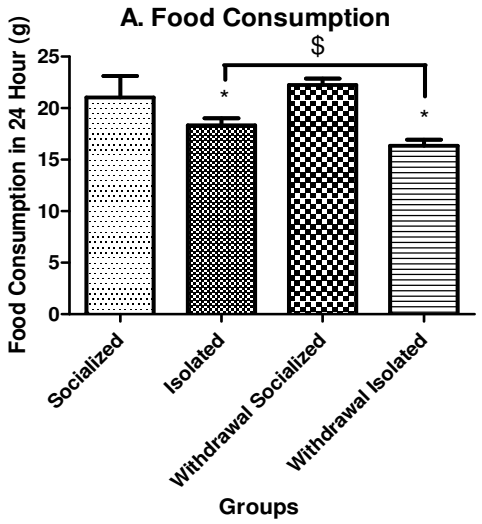
Fig. 4. Short term memory assessed by Y-maze / sec (n=8)
Data are represented as Mean ± SEM

3.4 Anxiety Level as Assessed by Novelty Suppressing Feeding Test (NSF)

During withdrawal, isolated rats demonstrated higher anxiety levels as compared to socialized rats. Also isolated rats demonstrated higher anxiety level than withdrawal isolated rats (Fig. 7).

3.5 Corticosterone Levels

Withdrawal socialized rats had lower corticosterone levels when compared to withdrawal isolated rats (Fig. 8).



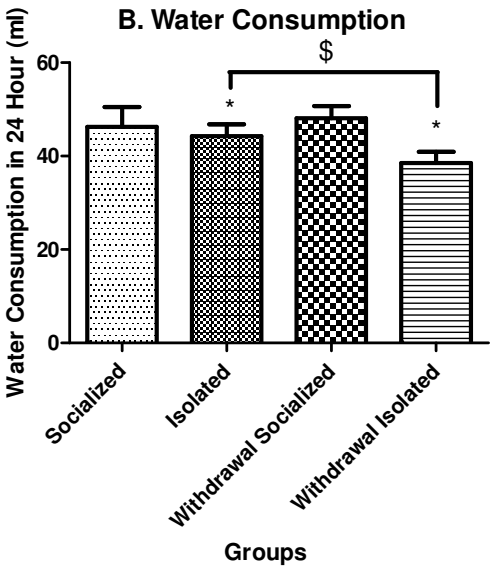


Fig. 5. A. Amount of food intake/g (n=8) B. Amount of water intake/ml (n=8)
Data are represented as Mean ± SEM

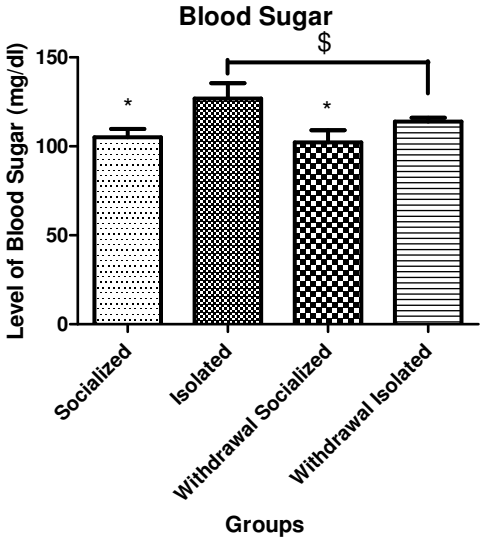


Fig. 6. Level of blood glucose mg/dl (n=8)
Data are represented as Mean ± SEM

3.6 Copper Level Assessment

In isolated and withdrawal isolated rats, plasma copper was higher as compared to socialized and withdrawal socialized rats, respectively. In addition, copper level was markedly higher in withdrawal isolated rats than in socialized rats. In isolated rats, plasma copper was more than withdrawal socialized rats (Fig. 9).

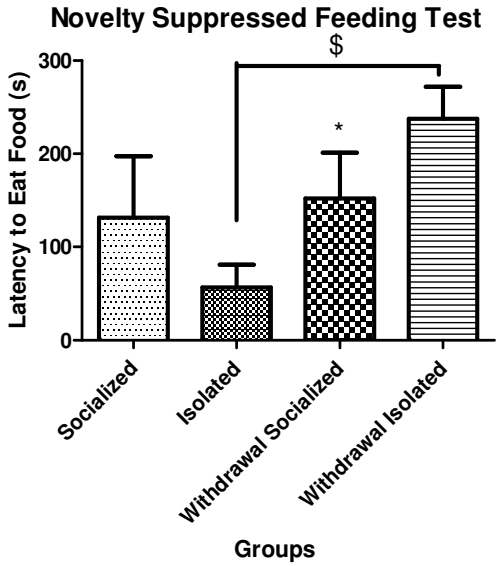


Fig. 7. Level of anxiety / sec (n=8)
Data are represented as Mean ± SEM

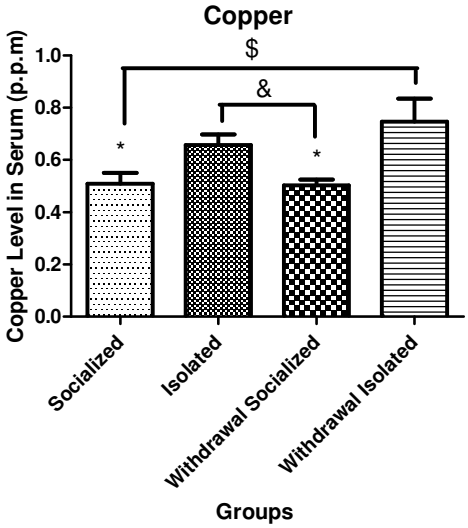


Fig. 9. Level copper in serum assessed by atomic spectrophotometer (n=6)
Data is represented as mean ± SEM. means *significant difference between adjacent groups and $ and & between those apart from each other*

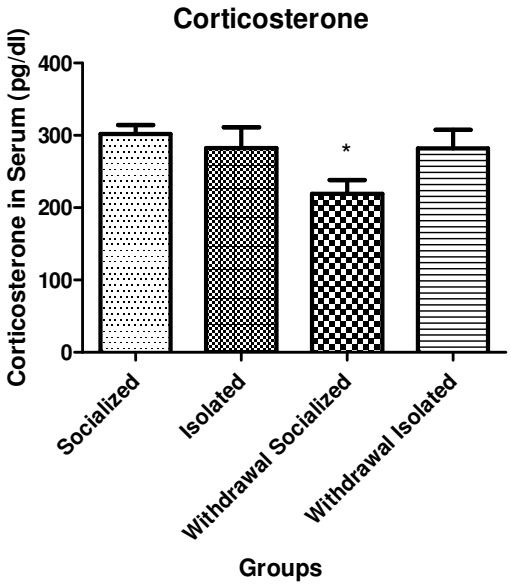


Fig. 8. Plasma level of corticosterone (pg/dl) (n=6)
Data are represented as mean ± SEM

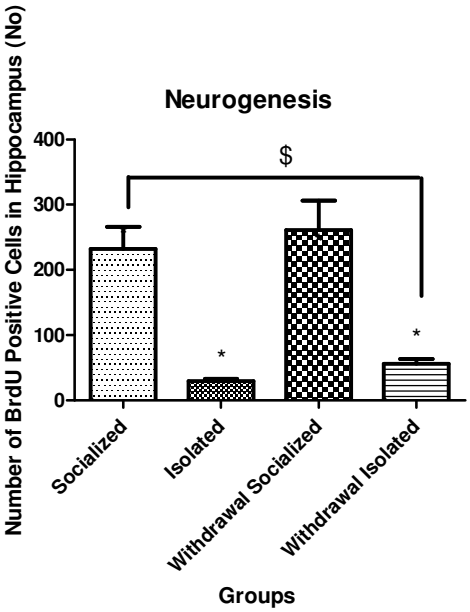


Fig. 10. Neurogenesis in dentate gyrus of hippocampus (n=8)
Data are represented as Mean ± SEM

3.7 Neurogenesis

During withdrawal, the number of BrdU positive cells in dentate gyrus of hippocampus was considerably lower in isolated rats in comparison to socialized rats. Also rats in withdrawal isolation had more neurogenesis than isolated rats (Figs. 10 and 11).

4. DISCUSSION

For the first time, our study shows that socialization during withdrawal period improves feeding behavior, neurogenesis, mood disturbances and stress responses. Furthermore,

we showed that withdrawal groups have worse prognosis than socialized and isolated groups.

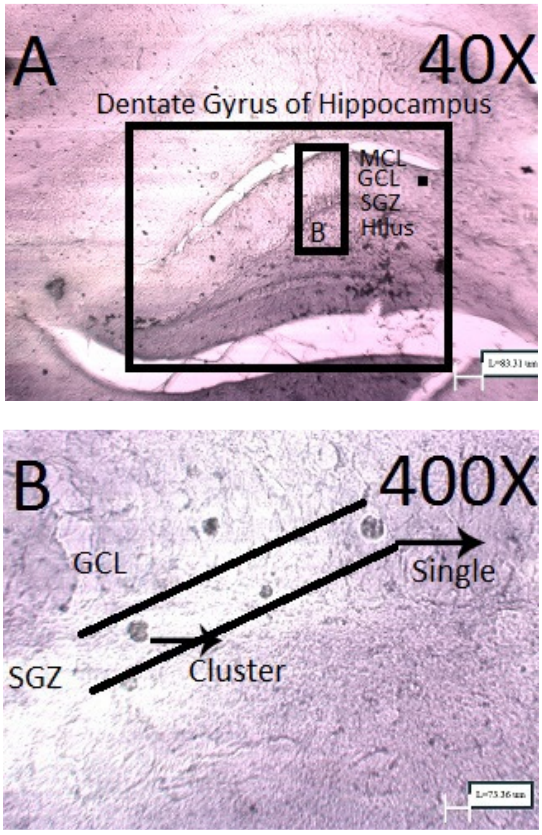


Fig. 11. A. Different parts of dentate gyrus of Hippocampus have been marked in picture. Counting of BrdU positive cell have been done in these areas. It has three parts: molecular cell layer (MCL) (outer (OML), middle (MML) and inner (IML)), granular cell layer (GCL) (sub granular zone (SGZ) and deep hilus) and hilus (40X) magnification B. BrdU positive cells have colored brown. They may be in single or cluster forms (400X magnification) (n=6). The two micrographs have been taken from dentate gyrus of withdrawal socialized rats in 40X and 400X respectively

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 [22]. In this study, we observed that hippocampal neurogenesis affects short-term food deprivation [23]. It has been suggested that BDNF plays an important role in regulating hippocampal neurogenesis and it may affect neuronal circuits involved in satiety [24]. In addition, neuropeptide Y - a neurotransmitter involved in neurogenesis and neuronal guidance, also controls food intake [9]. Neuropeptide Y can also alter food intake by changing emotional states that are regulated by the hippocampus. In this study it was assessed by novelty suppressed feeding test.

Emotional states can alter feeding behaviors by hormonal influences [25]. Hormones like glucocorticoids, leptin, adiponectin, resistin, and insulin affect hippocampal neurogenesis and this in return may influence the function of feeding center [26]. Furthermore, the depressed state can motivate an individual to take high-fat diet which can reduce hippocampal neurogenesis [27].

Adult hippocampal neurogenesis is highly influenced by isolation-induced stress [28]. 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). On the other hand, studies indicate that social defeat and restraint stress can reduce the rate of neurogenesis [29-31], but prolonged restraint stress may not affect it [32-34] Therefore, it seems that duration, frequency and intensity of stressors may influence neurogenesis.

There is ample evidence that chronic stress decreases hippocampal neurogenesis, especially in neonatal mice [35]. It may reduce survival and inhibit proliferation of new neurons [36]. Moreover, hippocampal - dependent learning as demonstrated by water maze training, causes acute downregulation of adult neurogenesis [37]. In accordance to previous studies, we found that social isolation - induced chronic stress reduces neurogenesis during drug withdrawal 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 [15]. Furthermore, elevated pro-inflammatory cytokines have been linked to neurodegeneration [38,39]. Following stress, IL-1 expression has shown to be dramatically enhanced in hypothalamus [40,41].

Adult hippocampal neurogenesis is vital for the regulation of feeding behavior and neuropeptide Y can potentiate both, neurogenesis and food intake. Hokfelt et al, showed that mice deficient in Y_1 or Y_2 receptor had fewer proliferating precursor cells and neuroblasts in subventricular zone and rostral migratory stream and fewer neurons in the olfactory bulb expressing calbindin, calretinin or tyrosine hydroxylase [9]. We found that socialization promotes food and water intake during withdrawal 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. [42]. 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 [42]. In a study, glucocorticoids have shown to increase food intake in rats by increasing sensitivity to leptin and insulin [43]. In addition to increased sensitivity to leptin and insulin, glucocorticoids also increase the sensitivity to melanocortin action [44]. Hence, in our study, reduced appetite can be partly attributed to changes in circadian rhythm and hormonal sensitivity caused by isolation.

The current literature lacks much information about the effect of diet and nutrition on adult hippocampal neurogenesis. One study found that high-fat diet impairs hippocampal neurogenesis in male rats [45]. However, other diets have not been studied yet. Neuronal lipoprotein lipase (LPL) is essential for regulating energy balance by hydrolyzing triglycerides. Picard et al, 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 [46]. Furthermore, caloric restriction and exercise enhances progenitor cell survival and proliferation, respectively [45,47], and social isolation can delay this exercise-induced neurogenesis [48]. The responding ability of new hippocampal neurons to triglycerides changes shows that new neurons may be affected by nutritional status affect [46]. Furthermore, Perera et al, reported that higher blood glucose levels were associated with higher rate of neurogenesis [24]. 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, both the hippocampus and hypothalamus are part of the limbic system with the appetite center located in the hypothalamus. Secondly, hippocampal projections spread to adjacent areas like feeding center [24]. In addition, a study shows that BDNF knock-out rats have poor regulation of food intake and demonstrate diminished hippocampal neurogenesis. [24,49]. We observed high glucose intake by isolated rats during withdrawal, which can be due to the increase in metabolic demand for restoring neurogenesis.

Leptin- an adipose-derived hormone affects hypothalamic receptors that control food intake. It also increases hippocampal cell proliferation by interacting with leptin receptors on hippocampal progenitor cells [24,50].

Ghrelin is a hormone and neuropeptide which is involved in regulating energy balance via hypothalamic circuits [51]. Ghrelin also plays an important role in regulating reward perception in dopamine neurons that link ventral tegmental area to nucleus accumbens [52]. However, the role of exogenous Ghrelin in promoting neurogenesis via regulating behavior needs to be investigated.

Independent of its cognitive functions, the hippocampus plays a distinctive role in mediating mood balance. The current literature demonstrates that selective impairment of hippocampal neurogenesis can exhibit a striking increase in anxiety-related behaviors [2, 53]. The 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 [54].

Social interaction profoundly affects neurogenesis and this effect can at least be

partly attributed to oxytocin [55]. A study suggests the therapeutic effect of oxytocin for treating amphetamine abuse [56].

During withdrawal period, we observed elevated corticosterone levels in isolated rats. It is in accordance with previous studies which have reported elevated corticosterone levels during substance abuse. Interestingly, increased corticosterone can lead to long-lasting alterations in social interactions and aggression [57]. Furthermore, chronically high corticosterone can reduce hippocampal neurogenesis which in turn can adversely affect serotonin levels and mood [15]. Yuan et al., demonstrated that exogenous corticosterone suppresses body weight gain and reduces feed and caloric efficiencies [58]. Our study suggests that corticosterone exerts its negative effects partly by reducing neurogenesis.

Copper is present throughout the brain but is most abundant in basal ganglia, hippocampus, and cerebellum Copper acts as a cofactor for many enzymes in brain such as tyrosinase, peptidylglycine α-amidating mono-oxygenase, copper/zinc superoxide dismutase, ceruloplasmin, hephaestin, dopamine-β-hydoxylase, and cytochrome *c* oxidase. Interestingly, imbalanced Cu homeostasis in brain, contributes to neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and sclerosis [59]. Furthermore, NMDA receptors also are regulated by this ion [60] and also NMDA receptor activation mediates copper homeostasis [61]. In this study, Cu levels were found to be higher in isolated animals as compared to control rats. Further, isolated and withdrawal isolated rats had higher Cu levels than isolated and withdrawal socialized rats, respectively. These results signify the importance of socialization. We found that withdrawal isolated rats had elevated Cu levels as compared to control rats, and this implies that in withdrawal period Cu increases. Copper probably affects neurogenesis and this in return, directly or indirectly via rewarding center may regulate addictive behaviors.

5. CONCLUSION

Socialization improves hippocampal neurogenesis and improves feeding behavior. Furthermore, socialization restores mood balance as seen by reduced anxiety levels. Socialization of addicts can result in good prognosis during withdrawal and can reduce risk of relapse in abstinence period.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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