VOLUME 10 NOMOR 2 DESEMBER 2023 ISSN 2548 – 611X

JURNAL
BIOTEKNOLOGI & BIOSAINS INDONESIA

Homepage Jurnal: http://ejournal.brin.go.id/JBBI/index

ENVIRONMENTAL ENHANCEMENT INCREASED SPATIAL MEMORY BUT NO SINGNIFICANT EFFECT ON ANXIETY IN RAT WITH PROPYLTHIOURACIL INDUCTION

Pengaruh Peningkatan Lingkungan terhadap Memori Spasial dan Kecemasan Tikus dengan induksi Propylthiouracil

[1]Zulkhah Noor*, [2]Dewi Alfika Puspitasari, [2]Oktavia Adiyani
[1]Department of Physiology, Faculty of Medicine and Health Sciences,
Universitas Muhammadiyah Yogyakarta.
[2]Medical Study Program, Faculty of Medicine and Health Science,
Universitas Muhammadiyah Yogyakarta
*Email: zulkhah.noor@umy.ac.id

ABSTRACT

This study aims to determine the effect of environmental enrichment on spatial memory and anxiety in Propylthiouracil (PTU)-induced thyroid disorder rats. The design of this study was an experimental post test and controlled group design to analyze differences in spatial memory in rats at the end of the study. The subjects in this study were normal rat pups and Rat with PTU induction. Subjects were divided into 4 groups namely, the control group, the normal group with environmental enrichment, the rat group with PTU induction, and the rat group with PTU induction with environmental enrichment. Each group consisted of 8 rats. At the time the rats were born, the rats were given 0.025% PTU which was mixed in their drink and given to the mother until the rats were born until they were 4 weeks old. Environmental enrichment was carried out for 6 weeks. The spatial memory test in Rat was carried out when the pups were 60 days old. Data analysis used One Way Annova, Kruskal Wallis, Post Hoc Test and Mann-Whitney Test. Enrichment of the environment increased the learning latency time of normal rats by 27.8 ± 1.509 seconds to 9.9 ± 4.434 seconds with memory retention increasing by 6.85% (p <0.05). Environmental enrichment in PTU-induced rats accelerated from 84.5 ± 8.70 to 77 ± 1.383 with memory retention increasing by 7.06% (p <0.05). Environmental enrichment did not significantly affect the behavior and anxiety of normal rats or PTU induced (p>0.05). Environmental enrichment to normal rats and impaired thyroid function can increase spatial memory but has no effect on reducing anxiety.

Keywords: *Environmental enrichment*, *PTU induction; spatial memory; Anxiety*

ABSTRAK

Penelitian ini bertujuan untuk mengetahui pengaruh pengayaan lingkungan terhadap memori spasial dan kecemasan pada tikus gangguan fungsi tiroid yang diinduksi Propylthiouracil (PTU). Penelitian ini merupakan eksperimental posttest and controlled group design untuk menganalisis perbedaan memori spasial dan kecemasan pada tikus di akhir penelitian. Subjek dalam penelitian ini adalah anak tikus dari induk normal dan anak tikus dari induk yang diinduksi PTU. Subyek dibagi menjadi 4 kelompok yaitu kelompok kontrol, kelompok normal dengan pengayaan lingkungan, kelompok tikus dengan induksi PTU, dan kelompok tikus dengan induksi PTU dan pengayaan lingkungan. Setiap kelompok terdiri dari 8 ekor tikus. Pada saat tikus dilahirkan, induk tikus diberi PTU 0,025% yang dicampurkan pada minumannya dan diberikan kepada induknya sampai anak berumur 4 minggu. Pengayaan lingkungan dilakukan selama 6

Received: *08 April 2023* ***Accepted***: *30 December 2023* ***Published***: *30 December 2023*

minggu. Tes memori spasial pada tikus dilakukan saat anak tikus berusia 60 hari. Analisis data menggunakan One Way Annova, Kruskal Wallis, Post Hoc Test dan Mann-Whitney Test. Pengayaan lingkungan mempercepat waktu latensi belajar tikus normal sebesar 27,8 ± 1,509 detik menjadi 9,9 ± 4,434 detik dengan retensi memori meningkat sebesar 6,85% (p <0,05). Pengayaan lingkungan pada tikus yang diinduksi PTU dipercepat dari 84,5 ± 8,70 detik menjadi 77 ± 1,383 detik dengan peningkatan retensi memori sebesar 7,06% (p <0,05). Pengayaan lingkungan tidak berpengaruh signifikan terhadap perilaku dan kecemasan tikus normal atau yang diinduksi PTU (p>0,05). Pengayaan lingkungan pada tikus normal dan gangguan fungsi tiroid dapat meningkatkan memori spasial namun tidak berpengaruh pada penurunan kecemasan

Kata Kunci: Pengayaan lingkungan, induksi PTU; memori spasial; Kecemasan

INTRODUCTION

The incidence of congenital hypothyroidism is estimated at 1: 2000-1: 4000 newborns (1). Congenital hypothyroidism early in life either permanently or transiently can inhibit growth and cause mental retardation (2). Congenital hypothyroidism in children can be caused by thyroid dysgenesis or dyshormogenesis or central disorders (3,4).

Based on the National Survey of IDD Mapping, Indonesia is included in the category of 21% mild endemic, 5% moderate endemic and 7% severe endemic (5). IDD cases in the Prambanan area were 83.5% of subjects with insufficient iodine intake, 15.7% of iodine deficiency and 13% of subjects with goiters (6). The incidence of congenital hypothyroidism in the Yogyakarta area is 1:1,500 babies suffering from sporadic congenital hypothyroidism and 1:300 babies suffering from transient congenital hypothyroidism due to iodine deficiency.

Apart from iodine deficiency, another cause of IDD is goitrogenic. Goitrogenic is a substance that inhibits iodine from entering the body Unprocessed food ingredients will retain their nutritional content better, but there are some vegetables that contain cyanogenic glycosides which are thiocyanate precursors (7). Thiocyanate is one of the goitrogenic detoxification results from cyanide which is perfectly expressed through urine. Thiocyanate works by inhibiting iodine uptake into the thyroid gland and interfering with thyroid peroxidase activity (Semba & Delange, 2008). Another thyroid function disorder is a disorder at one level of the hypothalamus-pituitary-thyroid gland axis, causing thyroid hormone deficiency (Carageorgiou *et al*., 2007).

Thyroid hormone deficiency can cause a slowdown in the formation of synapses, neurotransmitter formation, and myelin formation, causing increased nerve cell death due to imperfect nerve cell maturation (8). Thyroid hormone determines the subventricular zone neural stem cell phenotype of the rat brain. This hormone determines all stages of nerve cell development. Prolonged hypothyroidism reduces not only the number of neuroblasts but also mitochondrial activity. Mitochondrial metabolism is very important to support nerve cell growth at all stages of nerve cell biology (Gothié et al., 2017; Gothié et al., 2020).

Impaired growth of nerve cells will have an impact on decreasing cognitive function, impaired memory, learning difficulties, which is very necessary for someone in their activities. Restoration of nerve cell growth will restore memory and learning ability (11) memory is very important in cognitive processes (12)

Damage or incomplete nerve growth in hypothyroidism can be repaired by administering thyroid hormone replacement (13,14) and various activities that can stimulate nerves (15,16). Environmental enrichment plays a role in nerve growth and damage repair (17). Environmental enrichment can improve performance in spatial memory tests, induce neurogenesis in the hippocampus, increase survival of newly formed granule cells, and inhibit apoptosis or spontaneous neuronal cell death. Neurogenesis can occur in the hippocampus which is regulated by genetic and environmental factors (18).

Environmental enrichment can improve spatial memory associated with increased metabolic activation in the frontal and prefrontal cortex and decreased activation in the basolateral amygdala and hippocampus. Environmental enrichment consists of enhancing a combination of social relationships, physical exercise and social interaction, eliciting behavior modification and neurodevelopment (19). Therefore, a study was conducted using the environmental enrichment model as a way to improve spatial memory in PTU-induced thyroid disorder rats.

METHODS

This was an experimental post-test and controlled group design. Post-test to analyze changes or differences in spatial memory and anxiety in rats at the end of the study.

Subject Research and rearing

The subjects of this study were 8 Wistar rats weighing 210-230 grams, males weighing 290-310 grams obtained from the UGM Faculty of Pharmacy. Animal rearing is carried out at the UMY experimental animal laboratory. The mother rats were adapted in a large cage (100 x 80 x 80) cm for 8 days and mated at night while being observed. Mating rats were separated into cages measuring 40 cm x 30 cm x 15 cm until they gave birth and suckled. Husk is replaced every 3 days. Feed in the form of rat pellets ad libitum, drink ad libitum distilled water, light 12 hours light 12 hours dark, room with air blower, room temperature 25-28^{o}C.

Administration of PTU antithyroid

Four pregnant rats to be induced by thyroid disorders were given 0.025% PTU from the 5th day of pregnancy until weaning at 28 days (20), 4 pregnant rat were allowed to remain normal. A total of 16 normal rat pups and 16 rats with thyroid disorders were divided into 4 groups (N = 8) randomly grouped, namely normal, normal with environmental enrichment, PTU induced, PTU induced with environmental enrichment.

Environmental Enrichment

Environmental enrichment in the form of a relatively large cage, measuring (100 x 120 x 80) cm and inside is equipped with various tools that rats voluntarily use for exercise. The tools provided are spinning wheels, climbing logs and large dry leaves besides husks. Drinking food is placed above so that the rats have to climb to eat and drink. Placement of rat pups in enrichment cages from 21 days of age to 6 weeks later.

Spatial Memory Measurement

Spatial memory is memory that is formed related to space, area, recognizes shape, distance, and area, and knows direction or position. This memory ability was studied and measured using the Morris Water Maze method. Measuring the spatial memory of rats using the Morris Water maze hidden platform method which is a round pool of water with a diameter of 120-180 cm and a depth of 60 cm with water that is kept at room temperature and has a hidden platform. below the surface of the water. The latency time measurement for finding the platform was carried out 4 times a day in randomly selected quadrants, for 8 days and followed by the retention time measurement through a test probe for 90 seconds (21).

Anxiety measurement

Measurement of anxiety in rats using the Open Field Maze method which is an open square (1.5 x1.5 m) surrounded by a wall which on the floor is divided into a central zone and a peripheral zone. Rat were placed in the middle of an open space and released for 10 minutes and recorded. Each rat was assessed based on the number of Rat crossing, standing, grooming and the amount of feces (22). Apart from using an open field maze, rats were also tested using a Light Dark Box, a rectangular box that has dark and light spaces where there is a door to connect the two. Rat were released in the middle of the light box and recorded for 5 minutes. Count the rats in the light and dark rooms.

Statistical test using the normality test Shapiro-Wilk, One Way Annova and poshoc or Kruskal Wallis and Mann Whitney.

RESULTS

The body weight of the pups was measured at the age of 21 days before being placed in the environmental enrichment cage and on the last day the measurement of spatial memory, behavior and anxiety.

Table 1. Average of Rats' Body Weight

Group	Amount	Average body weight before treatment (gr)	Average body weight after treatment (gr)
Control normal	8	82,3 ± 19,93	117,6 ± 22,12
Normal with environmental enrichment	8	93,5 ± 25,02	111,9 ± 27,89
Rats with PTU induction	8	58 ± 13,14	79,6 ± 12,75
Rats with PTU induction with environmental enrichment	8	65,6 ± 9,36	85,1 ± 12,89

The results above show that there was an increase in the average body weight of the rats before and after treatment so that it can be said that the rats experienced growth during the study. The smallest mean body weight before and after treatment was found in Rat with PTU induction, namely 58 grams and 79.6 grams. The highest average body weight of rats before treatment was found in normal rats with environmental enrichment, namely 93.5 grams and the largest average body weight of rats after treatment was found in normal control rats, namely 117.6 grams.

Table 2. Learning Latency Time Results

Group	Amount	Latent Time of Day 1±SD (sec)	Latent Time of Day 8±SD (sec)
Control Normal	8	27,8 ± 1,509^{a}	7,7 ± 6,516^{a}
Normal with environmental enrichment	8	9,9 ± 4,434^{b}	7,3 ± 3,427^{a}
PTU induction	8	84,5 ± 8,704^{c}	63,5 ± 2,924^{c}
PTU induction with environmental enrichment	8	77 ± 1,383^{cd}	19,2 ± 1,035^{cd}
Kruskal-Wallis test		*p = 0,001*	*p = 0,001*

Note: the rank of the same letter indicates that there is no significant difference p≤0.05

The results showed that the smallest mean latency time of the first and last day was found in the group of normal Rat with environmental enrichment and the greatest in the group of Rat with PTU induction ($p<0.05$). The group of normal rats with environmental enrichment and the group of rats induced with PTU with environmental enrichment obtained a smaller average latency time, so it took a short time to find a platform compared to the group of Rat with PTU induction. The group of Rat with PTU induction obtained the greatest average latency time so it took longer to find a platform. The average latency time in the PTU-induced rat group with environmental enrichment showed that the rats could find the platform in less than 60 seconds, while the PTU-induced rat group still had difficulty finding the platform ($p<0.05$). On the last day, the group of rats induced by PTU experienced a slight decrease in time, while the group of rats induced by PTU with environmental enrichment experienced a significant decrease in time.

Table 3. Memory Retention Time Results

Group	Amount	Average Retention time ± SD (sec)	Spatial Memory Retention Time Percentage
Control Normal	8	27,9 ± 6.98708[a]	31%
Normal with environmental enrichment	8	34 ± 3.54965[a]	37,85%
PTU induction	8	19,8 ± 4.87338[c]	22%
PTU induction with environmental enrichment	8	26,2 ± 5.0776[abc]	29,06%
One Way Annova		*p = 0,001*	

Note: the rank of the same letter indicates that there is no significant difference p≤0.05

The smallest average time the rats could survive in the platform quadrant was found in the PTU-induced rat group and the largest was found in the normal rat group with environmental enrichment (p<0.05). The normal rat group and the normal rat group with environmental enrichment had a longer average time so that they were in the platform quadrant longer than the group of Rat with PTU induction (p<0.05). The average retention time of the PTU-induced rat group with environmental enrichment was able to match the normal control group (p>0.05). The group of rats induced by PTU with environmental enrichment experienced a non-significant increase in time compared to the group of rats induced by PTU (p>0.05).

Table 4. Average behavior of standing, crossing, and the amount of rat feces in the open field maze test

No	Rats group	Activity (Amount ± SD)		
		Stand	Cross	Defecation
1	Control Normal	28.75 ± 5.994[a]	6.75 ± 5.263[a]	1 ± 0.926[a]
2	Normal with environmental enrichment	35.9 ± 14.783[a]	6.9 ± 3.758[a]	1.8 ± 1.061[a]
3	PTU induction	28.5 ± 8.733[ab]	4.9 ± 1.773[a]	3.3 ± 1.309[ab]
4	PTU induction with environmental enrichment	20.125 ± 6.999[dbc]	6.5 ± 4.751[a]	3.5 ± 2.726[a]
Significancy		*Anova* *p = 0.001*	*Anova* *p = 0.211*	*Kruskal-Wallis* *p = 0.004*

Note: The same exponent of letters shows no significant difference.

Table 4 shows that all groups of rats in the crossing activity experienced no significant change (p=>0.05), while standing activity and the number of stool counts experienced a significant change (p=<0.05).

Table 5. The average dark and light times of rats in the dark light maze box

NO	Rats' group	*Dark Light Maze* ± %	
		Dark	Light
1	Control Normal	104.25 ± 34.75%[a]	195.75 ± 5.25% [a]
2	Normal with environmental enrichment	97 ± 32.33% [a]	203 ± 76.67% [a]
3	PTU induction	274.625 ± 91.54%[cb]	25.375 ± 8.46% [cb]
4	PTU induction with environmental enrichment	259 ± 86.33%[db]	41 ± 13.67% [db]
Significancy Kruskal-Wallis		*p = 0.000*	*p = 0.000*

Note: The same exponent of letters shows no significant difference.

Table 5 shows that all groups of mice in the dark and light experienced significant changes (p=<0.05).

The same rank in the congenital hypothyroid group as in the environmental enrichment congenital hypothyroid group showed no significance, so it can be interpreted that environmental enrichment does not have a tendency to reduce anxiety in congenital hypothyroid mice.

DISCUSSION

The normal body weight of the pups corresponds to the development of the Wistar rats from several laboratories (Janver Lab, 2019; NCKU, 2015). PTU-induced thyroid function disorder rats experienced growth retardation with significantly lower body weight than normal control rats. These results are in accordance with the results of another study (26), that decreased mitochondrial function reduces energy metabolism which has an impact on delaying organ growth and development and will reduce various body functions (10,27). The body weight of normal rats and thyroid disorders that were given environmental enrichment interventions showed an increase compared to those without intervention. The various physical activities carried out by rats stimulated by an enriched environment such as running in a rotary wheel, climbing, pushing dry leaves are thought to increase thyroid hormones such as rats doing treadmill or swimming exercises (28,29). This increase in thyroid function has an impact on increasing metabolism and improving body growth and development. It is like thyroxine therapy in hypothyroid patients (30).

The drawback of this study is that it does not measure thyroid hormone and TSH levels. Giving PTU at a level of 0.025% to pregnant sows in drinking water has made the rats hypothyroid (Hamoulli et al, 2007), resulting in the birth of hypothyroid rats with a decrease in serum fT4 levels of 12.3 ± 1.15 ng. Administration of PTU inhibits the production of new thyroid hormone in the thyroid gland by inhibiting the thyroid peroxidase enzyme. Inhibition of the thyroid peroxidase enzyme will reduce the conversion of iodide into iodine molecules so that the subsequent effect does not occur the attachment of iodine molecules to the amino acid tyrosine. Therefore, the new DIT (diiodotyrosine) or MIT (monoiodotyrosine) which are major constituents in the production of thyroxine (T4) and triiodothyronine (T3) are not produced). In addition, PTU acts peripherally by inhibiting the conversion of T4 to T3. This will decrease the thyroid hormone stored in the thyroid gland as well as circulating in the blood (31).

Hypothyroidism can also be induced by administering methimazole or carbimazole. The use of methimazole and carbimazole needs attention in pregnancy. Carbimazole has not been proven safe in pregnancy and has teratogenicity potential, in the form of cutaneous aplasia of the scalp, head and neck anomalies and others. Methimazole and carbimazole are contraindicated for use in pregnancy and should be replaced by propylthiouracil. Propylthiouracil has been shown to be safe for pregnant and lactating women, although it is transplacental and is excreted in breast milk in small amounts (32).

Memory testing in this study is in the form of spatial memory measurements. Spatial memory is memory related to field space, namely memory that directs a person to a location or place where an object is located, one's position, or the location of a city or area and the memory of spatial space forms a cognitive map ((33).. The memory system gradually matures over time early in development, and concomitant with the gradual accumulation of knowledge.Discrete spatial experience accelerates the functional maturation of the spatial memory system during childhood development, and this plays an important role in cognitive abilities and memory (34)

Giving PTU significantly increases the learning latency time, even the rats are not able to complete the task according to the allotted time. After studying for 8 days, the PTU-induced rats were still unable to complete the task properly with little memory retention. Giving environmental enrichment interventions will have an effect on improving the spatial memory of normal and hypothyroid rats by decreasing learning latency and increasing memory retention. The rat pups in the enrichment cage showed good learning abilities so they quickly learned environmental conditions and completed tasks well too. Environmental enrichment encourages active individuals to carry out neuromuscular activities continuously which have an impact on repairing nerves and muscles that experience impaired growth due to hypothyroidism. Exercise activity will emerge the maturation properties of prefrontal neurons by training repetitive neural networks in cognitive tasks (23) and mediating hippocampal cell neurogenesis with BDNF repair which plays a role in memory and cognition processes (16).

Environmental enrichment can improve spatial memory through the Brain-Derived Neurotropic Factor (BDNF) pathway. BDNF is a neurotropin that plays a role in synapse development, synaptic plasticity, induces neurogenesis and cognitive function (Hermanto, 2004). BDNF has a role in regulating cell survival and programmed cell death (apoptosis) during brain development. BDNF plays a role in the physiological function of the central nervous system, the development of cortical maturation and synaptic plasticity. Environmental enrichment can produce a variety of brain morphological changes in areas important for spatial learning and memory, such as the hippocampus and neocortex. Environmental enrichment will increase dendritic branching, synaptic contacts and neurotransmission, and neuron size in the rat neocortex (Rossi & Angelucci, 2006). The group of mice that were made hypothyroid and experienced failure in the growth and development of their brains, showed an increase in spatial memory after being given environmental enrichment. This is in line with sports games intervention for elementary school children (SD) every day for 30-60 minutes every day. Although sports games do not affect TSH levels and scores of elementary school children in GAKI endemic areas, they significantly increase BDNF levels (35).

Environmental enrichment is complex sensory-motor stimulation in which animals are provided with greater opportunities for physical exercise, various learning experiences and social interactions (36). The environmental enrichment paradigm is a combination of cognitive stimulation, exercise, and motor learning that will benefit memory and neural synaptic plasticity (37). Enrichment of the physical environment improves neurogenesis in the hippocampal dentate gyrus by increasing microRNA expression, by regulating miR-124 and miR-132, whereas enrichment of the social environment has an effect on brain plasticity and cognition (38)

Environmental enrichment stimulates the cognitive and memory systems through 2 pathways, namely stimuli to increase thyroid hormone production and direct stimulation to the nervous system which plays a role in cognitive abilities and memory. An increase in thyroid hormone is needed to increase the body's metabolism in the form of growth and development of neurons in the brain which functions as a center for thinking, learning and coordinating all activities, be it visual, spatial and cognitive (39–41). Growth, development and maturation of organ functions are highly dependent on energy metabolism which will function well in the presence of thyroid hormone (42,43)

Central nervous system damage results in cognitive impairment and depression (44). Mice with abnormally developed serotoninergic neurons and low serotonin production lead to aggressive behavior and increased anxiety (45). Serotonin is a monoamine neurotransmitter that acts as a sedative so it is needed to maintain emotional stability. Serotonin (5-HT) plays a role in appetite regulation which affects body weight, social behavior, locomotor function, sleep regulation, and heart rate. Reduced levels of serotonin in the brain can cause symptoms of depression and anxiety (Sadock et al., 2015). The decrease in appetite makes the congenital hypothyroid rats' weight smaller than normal mice.

The rat group in the standing activity experienced significant changes. This proves that there is a significant difference in rat activity. Research by Gong et al in 2018 using the Open Field Maze also states that environmental enrichment is a non-pharmacological method that inhibits anxiety and depression-like behaviors. Environmental enrichment as social and physical stimulation together provides support for treating anxiety disorders and increases brain plasticity in humans (Olff, 2012).

The behavior of animals standing in an upright vertical position is considered exploratory behavior and has been used as a measure of anxiety in the Open Field Maze Test (Ennaceur, 2014). The average standing activity of the normal rat group was higher than that of the congenital hypothyroid rat group. This means that the congenital hypothyroid rat group is less exploratory behavior due to increased anxiety than the normal rat group. In the normal rat group, environmental enrichment had a good effect, as evidenced by the enrichment group having more standing activity on average. The congenital hypothyroid group showed no effect of increasing standing activity. In general, rats with enriched environments show faster habituation to novelty than control rats (46). Research conducted by Gong et al in 2018 states that environmental enrichment is anxiolytic and antidepressant which can reduce anxiety and depressive behavior.

The crossing activity of the rat group did not change significantly, although the normal rat group had an average crossing activity of more than the congenital hypothyroid rat group. The mean activity across the environmental enrichment congenital hypothyroid rat group was greater than the congenital hypothyroid rat group. This suggests that the environment-enrichment congenital hypothyroid rat group was bolder. Some problems that can affect the results for example lighting conditions (47). The results obtained can be related to several parameters of the cage conditions, test time, protocol, and the selected rat strain (48). A reduction in anxiety-related behavior may occur because the rats lose tactile contact with the labyrinth walls and enter the center more easily. Anxious mice interfere with learning about context (49).

The defecation activity of the rat group experienced significant changes. Defecation is a measure of negative emotionality in rodents (50), and can be used to indicate anxiety levels in rats. Defecation behavior can indeed be a useful indicator of emotional anxiety in a relatively short test period (51).

Grooming activity was found more in the enrichment congenital hypothyroid rat group than in the congenital hypothyroid rat group. Several studies have found an increase in grooming and rearing in mice with an enriched environment (52). Grooming behavior can be observed when rats wash their front mouth or hind legs, wash their face, body and genitals (53). Time spent grooming is assessed as an index of self-care and motivational behavior (48). Decreased grooming can be interpreted as a loss of motivational behavior, considered a symptom of depression and anxiety (54)

Rat activity on the light and dark side experienced a significant difference. The average dark time in the congenital hypothyroid rat group was greater than in the environmental enrichment congenital hypothyroid rat group. Bright areas create an aversive environment and rats will change their behavior. Time spent will increase in dark areas. When mice are moved to a bright area, they will immediately move to a dark area (55). Another recent study found a similar environmental period of enrichment to anxiolytic in a rodent model of congenital anxiety abnormalities (56).

CONCLUSION

Environmental enrichment to normal rats and impaired thyroid function can increase spatial memory but has no effect on reducing anxiety

ACKNOWLEDGEMENT

Thanks to the medical and health sciences faculties for funding this research.

REFERENCES

Amisha F, Rehman A. Propylthiouracil (PTU). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK549828/

Ashokan A, Sivasubramanian M, Mitra R. Seeding Stress Resilience through Inoculation - PMC [Internet]. [cited 2023 Jun 10]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4736400/

Balietti M, Pugliese A, Fabbietti P, Di Rosa M, Conti F. Aged rats with different performances at environmental enrichment onset display different modulation of habituation and aversive memory. Neurobiology of Learning and Memory. 2019 May 1;161:83–91.

Barret KimE, Barman SM, Boitano S, Brooks HL. Ganong's review of medical physiology 24th edition.pdf [Internet]. Google Docs. 2012 [cited 2022 Sep 20]. Available from:

https://drive.google.com/file/d/0B1jPiTaWrcSXT3hBdnp0c0FaZ2s/view?usp=embed_facebook
Bayne K. Environmental enrichment and mouse models: Current perspectives. Animal Model Exp Med. 2018 Jul 28;1(2):82–90.
Bernal J. Thyroid Hormones in Brain Development and Function. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2023 Jun 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK285549/
Bowden SA, Goldis M. Congenital Hypothyroidism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 May 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK558913/
Brenes JC, Lackinger M, Höglinger GU, Schratt G, Schwarting RKW, Wöhr M. Differential effects of social and physical environmental enrichment on brain plasticity, cognition, and ultrasonic communication in rats: Environmental enrichment: Brain and behavior. J Comp Neurol. 2016 Jun 1;524(8):1586–607.
Chen W, Wang Z, Ma C, Ma X, Meng W, Yin F, et al. Tactile cues are important to environmental novelty during repeated open field tests. Behavioural Processes. 2023 Jan 1;204:104796.
Cicatiello AG, Di Girolamo D, Dentice M. Metabolic Effects of the Intracellular Regulation of Thyroid Hormone: Old Players, New Concepts. Frontiers in Endocrinology [Internet]. 2018 [cited 2023 Jun 10];9. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2018.00474
Contreras MP, Fechner J, Born J, Inostroza M. Accelerating Maturation of Spatial Memory Systems by Experience: Evidence from Sleep Oscillation Signatures of Memory Processing. J Neurosci. 2023 May 10;43(19):3509–19.
Costall B, Jones BJ, Kelly ME, Naylor RJ, Tomkins DM. Exploration of mice in a black and white test box: validation as a model of anxiety. Pharmacol Biochem Behav. 1989 Mar;32(3):777–85.
Depkes RI. Kementerian Kesehatan Republik Indonesia [Internet]. 2010 [cited 2023 May 25]. Available from: https://www.kemkes.go.id/article/view/13010200017/download-pusdatin-profil-kesehatan-indonesia-2010.html
Dewi YLR. Senyawa Goitrogenik dalam Bahan Makanan (Goitrogenik Substances in Foodstuffs). BIOEDUKASI. 2015 Aug 1;8(2):24.
Engle RW. Role of Working-Memory Capacity in Cognitive Control. Current Anthropology. 2010 Jun;51(S1):S17–26.
Farag EA, Filobbos SA, Afifi NM, Mahmoud ST, Alghandour SM. Thyroxine restores hippocampal neurogenesis and synaptogenesis in a male rat model of carbimazole-induced hypothyroidism: a histological study. Beni-Suef University Journal of Basic and Applied Sciences. 2023 Jun 6;12(1):57.
Gothié JD, Sébillot A, Luongo C, Legendre M, Nguyen Van C, Le Blay K, et al. Adult neural stem cell fate is determined by thyroid hormone activation of mitochondrial metabolism. Mol Metab. 2017 Aug 19;6(11):1551–61.
Gothié J, Vancamp P, Demeneix B, Remaud S. Thyroid hormone regulation of neural stem cell fate: From development to ageing. Acta Physiol (Oxf). 2020 Jan;228(1):e13316.
Hall JE. Guyton and Hall textbook of medical physiology. 13th edition. Philadelphia, PA: Elsevier; 2016. 1145 p.
Hamouli-Said Z, Tahari F, Hamoudi F, Hadj-Bekkouche F. Comparative study of the effects of pre and post natal administration of a thyroid drug on testicular activity in adult rat. Folia histochemica et cytobiologica. 2007;45(I):51–7.
Han Y, Yuan M, Guo YS, Shen XY, Gao ZK, Bi X. The role of enriched environment in neural development and repair. Front Cell Neurosci. 2022 Jul 21;16:890666.
Hayat NQ, Nadir S, Muneera MJ. The Effect of Hypothyroidism on the Body Weight of Adult Albino Wistar Rats.

Hu C, Luo Y, Wang H, Kuang S, Liang G, Yang Y, et al. Re-evaluation of the interrelationships among the behavioral tests in rats exposed to chronic unpredictable mild stress. PLOS ONE. 2017 Sep 20;12(9):e0185129.

Janver Lab. WISTAR Rat [Internet]. Janvier Labs. 2019 [cited 2023 Jun 9]. Available from: https://janvier-labs.com/en/fiche_produit/wistar_rat/

Kuo JY, Denman AJ, Beacher NJ, Glanzberg JT, Zhang Y, Li Y, et al. Using deep learning to study emotional behavior in rodent models - PMC [Internet]. 2022 [cited 2023 Jun 10]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9722968/

Kurniawan LB. Congenital Hypothyroidism: Incidence, Etiology and Laboratory Screening. INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY. 2020 Sep 30;26(3):375–80.

Kyriacou A, Kyriacou A, Makris KC, Syed AA, Perros P. Weight gain following treatment of hyperthyroidism—A forgotten tale. Clinical Obesity. 2019;9(5):e12328.

Lambert T, Fernandez S, Frick K. Different types of environmental enrichment have discrepant effects on spatial memory and synaptophysin level in female mice. Neurobiology of learning and memory. 2005 Jun 1;83:206–16.

Leggio MG, Mandolesi L, Federico F, Spirito F, Ricci B, Gelfo F, et al. Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. Behavioural Brain Research. 2005 Aug;163(1):78–90.

Lei X, Wu Y, Xu M, Jones OD, Ma J, Xu X. Physical exercise: bulking up neurogenesis in human adults. Cell & Bioscience. 2019 Sep 3;9(1):74.

Liu PZ, Nusslock R. Exercise-Mediated Neurogenesis in the Hippocampus via BDNF. Front Neurosci. 2018 Feb 7;12:52.

Liu YH, Zhu J, Constantinidis C, Zhou X. Emergence of prefrontal neuron maturation properties by training recurrent neural networks in cognitive tasks. iScience. 2021 Oct 22;24(10):103178.

Livingston J, Nelson P, Karthikeyan S, Antonescu S, Jeffers M, Marzolini S, et al. Exercise and Environmental Enrichment as Enablers of Task-Specific Neuroplasticity and Stroke Recovery. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2016 Feb 12;13.

Mishra R, Phan T, Kumar P, Morrissey Z, Gupta M, Hollands C, et al. Augmenting neurogenesis rescues memory impairments in Alzheimer's disease by restoring the memory-storing neurons. Journal of Experimental Medicine. 2022 Aug 19;219(9):e20220391.

Mora-Gallegos A, Fornaguera J. The effects of environmental enrichment and social isolation and their reversion on anxiety and fear conditioning. Behavioural Processes. 2019 Jan 1;158:59–69.

Mutalazimah M, Mulyono B, Murti B, Azwar S. Asupan Yodium, Ekskresi Yodium Urine, dan Goiter pada Wanita Usia Subur di Daerah Endemis Defisiensi Yodium. Kesmas: National Public Health Journal. 2013 Oct 1;8(3):139.

NCKU. Weight to Age-in-Week Table for Rat [Internet]. 2015 [cited 2023 Jun 9]. Available from: https://animal.ncku.edu.tw/p/412-1130-16363.php?Lang=en

Noli L, Khorsandi SE, Pyle A, Giritharan G, Fogarty N, Capalbo A, et al. Effects of thyroid hormone on mitochondria and metabolism of human preimplantation embryos. Stem Cells. 2020 Mar;38(3):369–81.

Noor Z, Agustiningsih D, Soesatyo MH, Soejono SK. The effect of swimming exercise on thyroid function, spatial memory and anxiety in normal and propylthiouracil-induced hypothyroidism in Wistar rats. Physiology and Pharmacology. 2021 Sep 10;25(3):231–41.

Noor Z, Safira I, Darmawati I. Sports Games towards Intelligence and Nerve Development of Children in Iodine Deficiency Endemic Area. 2023;4(1).

Núñez B, Martínez de Mena R, Obregon MJ, Font-Llitjós M, Nunes V, Palacín M, et al. Cerebral Cortex Hyperthyroidism of Newborn Mct8-Deficient Mice Transiently Suppressed by Lat2 Inactivation.

Plateroti M, editor. PLoS ONE. 2014 May 12;9(5):e96915.

Prezioso G, Giannini C, Chiarelli F. Effect of Thyroid Hormones on Neurons and Neurodevelopment. Hormone Research in Paediatrics. 2018 Aug 29;90:1–9.

Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis. 2010 Jun 10;5:17.

Remaud S, Gothié JD, Morvan-Dubois G, Demeneix BA. Thyroid Hormone Signaling and Adult Neurogenesis in Mammals. Front Endocrinol (Lausanne). 2014 Apr 28;5:62.

Sadler ME, Miller CJ. Performance anxiety: A longitudinal study of the roles of personality and experience in musicians. Social Psychological and Personality Science. 2010;1:280–7.

Samsudin M, Kumorowulan S, Supadmi S. Nilai Diagnostik Indikator Fisik Dibandingkan Baku Emas Untuk Menegakkan Diagnosis Terduga Kretin Pada Batita. Indonesian Journal of Micronutrition. 2014;5(2):149801.

Seibenhener ML, Wooten MC. Use of the Open Field Maze to Measure Locomotor and Anxiety-like Behavior in Mice. J Vis Exp [Internet]. 2015 Feb 6 [cited 2018 Oct 31];(96). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4354627/

Seibenhener M, Wooten MC. oen field anxiety rat journal - Google Search [Internet]. 2015 [cited 2023 Jun 10]. Available from: https://www.google.com/search?q=oen+field+anxiety+rat+journal&oq=oen+field+anxiety+rat+journal&aqs=chrome..69i57j33i10i160l2.149236633j0j15&sourceid=chrome&ie=UTF-8

Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK500006/

Shin MS, Ko IG, Kim SE, Kim BK, Kim TS, Lee SH, et al. Treadmill exercise ameliorates symptoms of methimazole-induced hypothyroidism through enhancing neurogenesis and suppressing apoptosis in the hippocampus of rat pups. International Journal of Developmental Neuroscience. 2013 May 1;31(3):214–23.

Simon A, Zacharin M. Chapter 3 - Thyroid Disorders. In: Zacharin M, editor. Practical Pediatric Endocrinology in a Limited Resource Setting [Internet]. San Diego: Academic Press; 2013 [cited 2023 Jun 10]. p. 69–95. Available from: https://www.sciencedirect.com/science/article/pii/B9780124078222000037

Terry AV. Spatial Navigation (Water Maze) Tasks. In: Buccafusco JJ, editor. Methods of Behavior Analysis in Neuroscience [Internet]. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2009 [cited 2023 Jun 9]. (Frontiers in Neuroscience). Available from: http://www.ncbi.nlm.nih.gov/books/NBK5217/

Volve KD. Altered Brain Functioning May Explain Cognitive Difficulties and Depression After Thyroid Hormone Withdrawal Following Thyroidectomy [Internet]. 2018 [cited 2023 Jun 10]. Available from: https://pro.endocrineweb.com/hyperthyroidism/altered-brain-functioning-may-explain-cognitive-difficulties-depression

Williams BM, Luo Y, Ward C, Redd K, Gibson R, Kuczaj SA, et al. Environmental enrichment: Effects on spatial memory and hippocampal CREB immunoreactivity. Physiology & Behavior. 2001 Jul;73(4):649–58.

Willner P. The chronic mild stress (CMS) model of depression: History, evaluation and usage. Neurobiology of Stress. 2017 Feb 1;6:78–93.

Yavuz S, Salgado Nunez del Prado S, Celi FS. Thyroid Hormone Action and Energy Expenditure. J Endocr Soc. 2019 May 16;3(7):1345–56.