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Effects of sertraline on episodic memory in experimental model of chronic mild stress model of depression

Hatice Solak[a,*], Zulfikare Isik Solak Gormus[b], Raviye Ozen Koca[b], Ayse Ozdemir[b], Mehmet Sinan Iyisoy[c], Ercan Kurar[d], Selim Kutlu[b]

[a] *Kütahya Health Science University, Faculty of Medicine, Department of Physiology, Kütahya, Türkiye*
[b] *Necmettin Erbakan University, Meram Faculty of Medicine, Department of Physiology, Konya, Türkiye*
[c] *Necmettin Erbakan University, Meram Faculty of Medicine, Department of Medical Education and Information, Konya, Türkiye*
[d] *Necmettin Erbakan University, Meram Faculty of Medicine, Department of Medical Biology, Konya, Türkiye*

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Abstract

Aim: Individuals with depression have cognitive deficits, including diminished thinking and concentration ability, as well as memory difficulties. Certain antidepressants used for depression are recognized to influence cognitive functions, including learning and memory positively. We aimed to examine the impact of sertraline on hippocampus cell proliferation and cognitive functions, including learning and memory, within a chronic mild stress (CMS) model.

Materials and Methods: 48 rats were divided into four groups: C, CMS, CMS+S, and S. CMS groups were subjected to various stressors for 15 days. S was delivered at a dosage of 10 mg/kg/day for a duration of 15 days using an osmotic minipump. On day 15, a forced swim test (FST), open field test (OFT) were conducted. The OFT, elevated plus maze (EPM), FST and novel object recognition test (NORT) were conducted to assess the efficacy of S. Animals were beheaded, and hippocampal tissues were excised. qRT-PCR was used to assess the expression levels of genes (BDNF, NeuN, MASH1). One-way ANOVA was used for statistical analysis.

Results: In the CMS group, there was a significant decrease in the percentage and speed of OFT movement compared to the control ($p<0.001$).There was a significant decrease in swimming, climbing and immobilization times in the depression group compared to the other groups. In the long-term memory analysis, a significant increase was observed in the recognition and discrimination index in the CMS+S group compared to the CMS group ($p<0.01$). BDNF, NeuN and MASH1 gene expression levels in hippocampal tissues showed a significant decrease in the depression group and a significant increase in the CMS+S group ($p<0.05$).

Conclusion: The study shows that sertraline in the treatment of depression is beneficial in improving cognitive abilities which is confirmed by the increasing gene expression. It is thought that serotonin improves long-term memory and may positively affect brain precursor cell formation.

Introduction

Depression is a prevalent psychiatric condition that has a toll on 350 million individuals globally [1]. Depression is a mood dysfunction characterised by persistent feelings of sadness, emptiness or hopelessness. Depression can affect various aspects of daily life, including emotions, thoughts, sleep patterns, eating habits, and work productivity [2]. Although the precise origins of depression are not well comprehended, it is believed that a mix of psychological, environmental, and biological variables play a role in its development [3]. These elements may include genetics, brain chemistry, trauma, life events, and other factors. Depression is linked to a spectrum of symptoms, including emotional manifestations such as sadness and despair as well as somatic manifestations such as alterations in food-eating beahvior and disturbances in sleeping patterns [2]. Some symptoms can be operational and measurable, making them suitable for evaluation in laboratory animals. These could include behaviors like changes in eating patterns, sleep disturbances, and cognitive alterations [3]. The examination of depression in laboratory animals has provided researchers with valuable insights into the

*Corresponding author:
Email address: hatice.solak@ksbu.edu.tr (Hatice Solak)

biological foundations of the condition and facilitated the development of viable remedies. Animal models can mimic certain aspects of depression-like behavior, which can aid in testing new therapies and understanding the neurobiological mechanisms involved [4]. Stress is believed to be a major contributor to the development of depression. Prolonged exposure to stressful events, particularly when coupled with genetic vulnerability, can heighten the likelihood of developing severe depression [5]. Environmental stressors can affect biological systems, especially the HPA axis. The brain regions mentioned are linked to the regulation of emotions, mood, and cognitive abilities [4]. Alterations in these regions are associated with the emergence of depressive symptoms. This axis governs the body's physiological reaction to stress. Stress can lead to the excessive secretion of glucocorticoids, such as cortisol, which are crucial to the organism's stress response. Stress impacts both hormonal systems, notably the HPA axis, and cerebral regions, including the limbic system and cortical areas.

Research with animal models, specifically mice, has shown that chronic stress paradigms, including chronic unpredictable stress and CMS, can lead to behavioral changes that mimic hopelessness and cognitive deterioration, both of which are characteristic of depression. The effects are believed to be caused by the overactivity of the HPA axis and the increased production of corticosterone [6,7]. Researchers have demonstrated that rats subjected to chronic mild stress model protocols exhibit behavior-related, neurochemical, neuroendocrine system, and neuroimmune changes analogous to those seen humans with depression. Thus, the CMS model established by Willner et al. [8] effectively meets numerous essential criteria to an animal model of depressed [8, 1]. CMS exposure prolongs immobility duration in rats during the FST. Traditional antidepressants, such as tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), help alleviate symptoms of depression caused by CMS [9]. Recent studies have focused on understanding how the brain carries out learning and memory that are considered to be advanced cognitive processes. Additionally, researchers have investigated the impact of medicines on these cognitive functions. Depression causes cognitive impairments, including reduced cognitive abilities such as focused thought and sustained attention, which in turn leads to impaired memory. An evident correlation between depression and cognitive impairment has been documented [10]. Short-term memory allows a person to recall numbers or events after thinking about them continuously for a few seconds or a few minutes, such as remembering 7 to 10 digits in a telephone number. Short-term memory can be explained by presynaptic facilitation or inhibition. These events take place at synapses located on presynaptic endings and not on the next neuron. Neurotransmitters released from such endings cause facilitation or inhibition, often lasting seconds or even minutes. Such circuits can lead to short-term memory [11]. Short-term memory covers the time it takes for ongoing events to be consolidated and translated into remote, long-term memory. At this stage, short-term memory is highly susceptible to alteration and can be erased. On the other hand long-term memory has remarkable durability against deletion and persists even under substantial brain trauma [12]. The episodic memory is a kind of the memory that is necessary to remember personally experienced events or where, when and what happened. [13]. Adult neurogenesis is a progressive process that occurs in various regions of the brain, including the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. Neural progenitor cells from these regions proliferate and migrate to the granule cell layer of the olfactory bulb and dentate gyrus which is their final destination. In this process, they undergo differentiation to generate new neurons and then integrate into pre-existing circuits [14]. The processes governing the control of hippocampus neurogenesis are currently being studied. A recent study indicated that both the cAMP cascade and BDNF have a role in the regulation of neurogenesis, which is enhanced by persistent antidepressant medication. The activation of the cAMP pathway or exposure to BDNF has been documented to enhance neuronal differentiation of progenitor cells and promote neurite outgrowth in vitro [15]. This study sought to examine the potential effects of sertraline on the limbic system in rats exhibiting depression-like behaviour. The research assessed the expression levels of particular biomarkers linked to neurogenesis in the hippocampus within an animal model of chronic mild stress administered sertraline.

Materials and Methods

Statement of ethics

Approved by the Ethics Committee with reference number 2021-029.

Experimental protocol

Animals

In this study we used 48 adult male Wistar albino rats, each aged 6 months. The rats were classified into four separate groups: The control group (n=12, C) recieved a solvent (DMSO) subcutaneously using an osmotic minipump.

The Chronic Mild Stress group (n=12, CMS) established a depression model in animals by the performing a CMS protocol. The DMSO solvent was administered subcutaneously via an osmotic minipump.

In the CMS + Sertraline group (n = 12, CMS+S), Sertraline was administered via osmotic minipump at a dose of 10 mg/kg per day with the CMS protocol.

The Sertraline group (n=12, S) recieved Sertraline (10 mg/kg/day) via an osmotic minipump (Alzet 2002, Alza Corp., Palo Alto, CA).

Chronic mild stress (CMS) protocol

The CMS procedure employed in the current investigation was adapted from the protocol proposed by Wilner [7]. The model's duration was 30 days, accompanied by behavioral testing. In Figure 1, it is seen that the antidepressant therapy persists for 15 days until the animals are decapitated. The CMS paradigm commenced on the second day of the trial. On the fifteenth day, the forced swimming stress training phase was conducted. This practice is also

regarded as a stressor. The stress model was maintained for 12 days following the installation of the osmotic pump. Behavioral assessments were conducted on the subsequent days. Stressors were not administered on the days when behavioral assessments were performed (Table 1). Information is provided in the Supplementary Methods [16].

Behavioral tests

The model was subjected to a series of behavioural evaluations, comprising the OFT, FST, EPM, and NORT. The tests were performed to assess locomotor activity, anxiety and depression-like behaviors, as well as learning and memory once the model was established and the pharmacological therapy was administered. These methodologies for assessing behavior have been recorded in prior studies. Consult further methods for further behavioral details [16]. The behavioral assessments were recorded and evaluated utilizing the Ethovision Video Monitoring System XT11 Netherlands.

New objectrecognition test (NORT)

NORT is performed in an open arena featuring two identical objects, usually composed of plastic, glass, or metal, and sufficiently substantial to resist displacement by the animal. In the spatial version, the animal explores the objects freely. After a delay, one object is moved to a new location within the arena. Rodents typically prefer to explore the moved object, indicating spatial memory. The non-spatial version is similar, but instead of moving an object, one object is replaced with a novel object. Rodents are anticipated to allocate increased time investigating the novel object, indicating recognition memory. In both versions, the duration of exploration of each object is recorded to assess memory [17].

The NORT assessed short-term and long-term episodic memory in rats, using a five-phase protocol: habituation, familiarization, long-term memory assessment, short-term memory assessment and a final recognition phase. Every phase consumed 5 minutes and was recorded using Ethovision XT11 software (Noldus, Netherlands) in a black Plexiglas arena (80 x 80 x 40 cm). During the short-term memory evaluation (four hours post-familiarization), one object was substituted with a novel object. In the long-term memory assessment (24 hours post-familiarization), the original object was substituted with a distinct novel object. Objects and the arena were sanitised with 70% ethanol between experiments. Discrimination and recognition indices were calculated using object interaction durations recorded by the software.

Recognition index = New object / (New object + Familiar object)

Discrimination index= (New object-Familiar object) / (New object+ Familiar object).

Measurement of serum levels of corticosterone

Serum corticosterone levels were assessed using the methodology established by Sahin et al. [18].

Concluding the experiment and obtaining biological specimens

Following behavioral evaluations, the rats were weighed and then euthanized under anesthesia. Their hippocampi were dissected over frozen dry ice in accordance with the Paxinos and Watson rat brain atlas. Hippocampal tissues were stored in cryotubes and snap-frozen in fluid nitrogen before being transplanted to -80 degrees Celsius for for a long time storage.

Analysis of gene expression

The procedures for total RNA extraction, quality assessment, and removal of gDNA contamination from hippocampal tissue samples were previously described and are detailed in the Supplementary Methods [16].

Primary sequence

The primers for the target and reference genes (PGK1, CycA) employed in quantitative real-time PCR (qRT-PCR) analysis are detailed in Table 2. The primer designs were created with the IDT PrimerQuest software (https://eu.idtdna.com/site) and sourced from the literature [19,20].

Reverse transcription reaction

cDNA was synthesized from the quality-controlled RNA samples using the manufacturer's technique. To produce single chain cDNA from 2 µg/20 µl total RNA, 1 µl Oligo dT and 1 µl Random hexamer were combined with 2 µg/20 µl total RNA and incubated in a water bath at +70 ° C for 5 minutes. Subsequently, 8 µl of 5X cDNA reaction mixture, 2 µl RNAse inhibitor, and 4 µl dNTP were added and maintained in a water bath at +25 ° C for 5 minutes. Subsequently, 2 µl of Reverse Transcriptase enzyme was introduced and incubated in a water bath at +25 ° C for 10 minutes, followed by incubation at +37 ° C for 60 minutes. The reaction was halted at a +70 ° C water bath for 10 minutes. The cDNA samples were preserved at -20 ºC for future utilisation.

Real-time quantitative polymerase chain reaction (qPCR)

Quantitative measurement of target and reference gene expression was conducted utilizing a real-time PCR apparatus (Bio-Rad CFX Connect Real-Time PCR System). SyberGreen, a dye that attaches to double-stranded DNA, was utilized for the reaction. In summary, 10 µl of 2X SyberGreen master mix, 5 pmol of forward primer, 5 pmol of reverse primer (refer to Table 2), 2 µl of cDNA, and ddH2O were combined to achieve a total volume of 20 µl, followed by the execution of the polymerase chain reaction. The reaction temperature profile consisted of an initial 10 minutes at 95 ° C, followed by 40 cycles of 95 ° C for 30 seconds, 60 ° C for 30 seconds, and 72 ° C for 30 seconds. Furthermore, a melting curve study was conducted by heating to 95 ° C for 1 minute, followed by a progressive temperature increase back to 95 ° C after cooling to 55 ° C. Threshold cycle (Ct) values acquired from the real-time PCR apparatus were documented. To verify the accuracy of the products generated from real-time

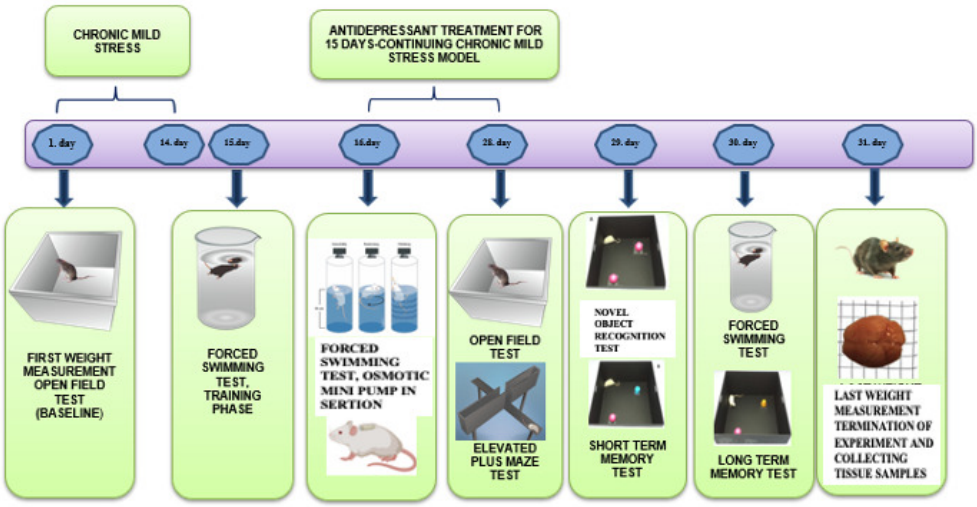

Figure 1. Schematic representation of experimental protocol.

Table 1. Scheme for the Chronic Mild Model Experiment.

	Morning			Noon			Night		
Day	Hour	Stressor	Duration	Hour	Stressor	Duration	Hour	Stressor	Duration
1	09.00	Restraint stress	45 minutes	01.00	Noise	4 hours	04.00	Food deprivation	All night
2	10.00	Wet Cage	7 hours				04.00	Light on	All night
3	09.00	FST	10 minutes	03.00	Restraint stress	45 minutes			
4	11.00	Inclined Cage	7 hours						
5	09.00	Noise	4 hours	02.00	FST	10 minutes	04.00	Food deprivation	All night
6	09.00	Wet Cage	7 hours				04.00	Light on	All night
7	10.00	Inclined Cage	7 hours						

Table 2. Primer sequences of genes used in qPCR analysis of hippocampus tissues.

Gene	Primer sequence (5'→3')	PCR product (bc)	Reference
BDNF	CTGAGCGTGTGTGACAGTATTA GGGATTACACTTGGTCTCGTAG	153	[19]
Nestin	CACACCTCAAGATGTCCCTTAG AGGTACTGGTCCTCTGGTATC	166	[19]
NeuN	GGCAAATGTTCGGGCAATTC GATCGTCCCATTCAGCTTCTC	140	[19]
Neuritin	TCGCGGTGCAAATAGCTTAC CGGTCTTGATGTTCGTCTTGTC	152	[19]
CycA	TATCTGCACTGCCAAGACTGAGTG CTTCTTGCTGGTCTTGCCATTCC	126	[20]
PGK1	ATGCAAAGACTGGCCAAGCTAC AGCCACAGCCTCAGCATATTTC	104	[20]

PCR, the samples were subjected to electrophoresis on a 2% agarose gel at 120 volts for 30 minutes and thereafter analysed.

Statistical analysis

Continuous data are represented by mean and standard deviation, while categorical variables are represented by frequency and percentage. The contiuous variables were analysed using ANOVA and mixed effects models. The Posthoc Tukey test or mean- comparisons with Tukey modifications were employed. The studies were performed utilising R version 4.3.2 (R Core Team, 2024). A significance level of $p<0.05$ was considered statistically significant. The preliminary phase of analysing gene expression data involved normalising the Ct values of the target genes relative to the Ct values of the reference genes PGK1 and CycA. This facilitated the calculation of 2 (-ΔCt) values, indicative of the gene expression levels. The 2(-ΔCt) val-

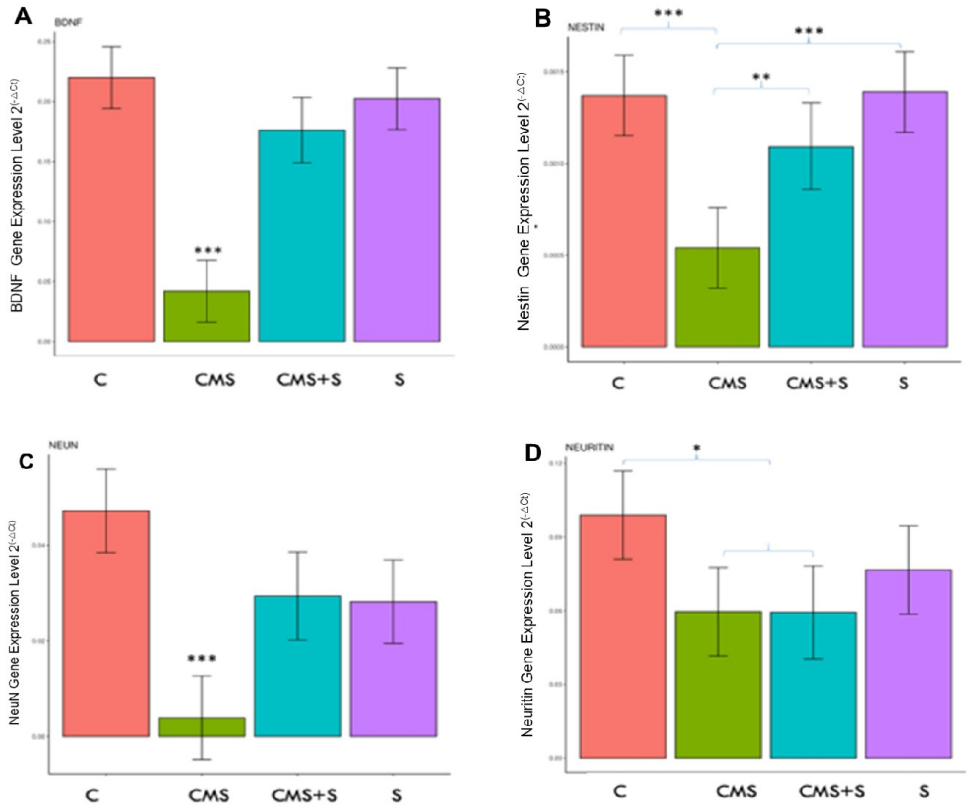

Figure 2. A BDNF expression levels in hippocampus tissue of control (C), CMS, CMS+sertraline (CMS+S), and sertraline (S) groups. Gene expression 2(-ΔCt) levels were compared by one-way analysis of variance (***p<0.001), (Comparison of CMS group with other groups). B Nestin expression levels in hippocampus tissue of control (C), CMS, CMS+sertraline (CMS+S), and sertraline (S) groups. Gene expression 2(-ΔCt) levels were compared by one-way analysis of variance (** p<0.01) (***p<0.001). C NeuN expression levels in hippocampus tissue of control (C), CMS, CMS+sertraline (CMS+S), and sertraline (S) groups. Gene expression 2(-ΔCt) levels were compared by one-way analysis of variance (***p<0.001), (Comparison of CMS group with other groups). D Neuritin expression levels in hippocampus tissue of control (C), CMS, CMS+sertraline (CMS+S), and sertraline (S) groups. Gene expression 2(-ΔCt) levels were compared by one-way analysis of variance (*p<0.05), (Comparison of CMS+ CMS+S group with other groups).

ues were analyzed for differences across groups using a one-way analysis of variance. Graphs illustrating the standard error of the mean squares for the relevant variables were generated. According to the post-hoc power analysis, the effect size (Cohen's f) obtained in the study was 0.901, the significance level was determined as (α=0.05) and the targeted statistical power (1-β) was calculated as 99.4%. Post-hoc power analysis showed that the study had an extremely high statistical power of 99.4%. These results reveal that our study is strong and reliable in detecting differences between groups.

Results

Open field test (OFT) assessments on days 1 and 28 revealed a significant decrease in distance moved, velocity, and percentage of movement in the chronic mild stress (CMS) group compared to baseline (day 0) (Table 3). Post hoc analysis using Tukey-adjusted least squares means comparisons after mixed-effects models confirmed a significant reduction in distance moved between day 0 and day 28 in the CMS group (p=0.017). Pairwise comparisons also showed a significant decrease in distance moved in the CMS group at day 28 (p=0.012). Furthermore, a significant decrease in the percentage of movement was observed in the CMS group at day 28 (p<0.001).

Following the OFT, the EPM was administered. Analysis of the percentage of time spent in open arms revealed a significant increase in both the sertraline-only group and the CMS+sertraline (CMS+S) group compared to the other groups. (p<0.01) (Table 4).

FST: In the FST, immobility time, swimming time, climbing time, and total movement were assessed on days 15 and 30 (Table 5). Tukey-adjusted post hoc least squares means comparisons following mixed-effects models revealed several significant differences:

Day 15:

- Swimming behavior was significantly decreased in the CMS and CMS+S groups compared to the control (C) and sertraline-only (S) groups (p=0.043).
- Climbing behavior was significantly decreased in the CMS and CMS+S groups compared to the C and S groups (p=0.035, 0.003, 0.001, and <0.001, respectively).
- Immobility time was significantly increased in the CMS and CMS+S groups compared to the C and S groups (p<0.001).

Day 30:

- Swimming behavior was significantly increased in the CMS+S and S groups compared to the other groups (p<0.001).

Table 3. Summary of the results of the OFT tests.

	0 day Mean±SD	28th day Mean±SD	p value
Control			
Distance Moved (cm)	1.142.91±426.18	985.86±362.94	0.462
Velocity(sn)	5.51±2.20	3.22±1.68	0.020*
Movement (%)	3.15±0.90	3.35±1.66	0.848
Chronic Mild Stress			
Distance Moved (cm)	894.50±197.18	523.53±346.01	0.017
Velocity(sn)	6.32±2.46	3.01±2.23	<0.001***
Movement (%)	3.52±1.27	1.07±1.14	<0.001***
Chronic Mild Stress +Sertraline			
Distance Moved (cm)	994.72±266.51	829.10±272.97	0.424
Velocity(sn)	7.51±2.90	4.30±2.00	0.001**
Movement (%)	3.40±1.08	1.89±0.53	<0.001***
Sertraline			
Distance Moved (cm)	1.192.47±325.65	948.84±404.94	0.160
Velocity(sn)	6.30±1.60	5.24±3.45	0.411
Movement (%)	3.29±0.71	2.39±0.53	0.042*

(*p<0.05). (**: p<0.01, ***: p<0.001). Tukey adjusted post hoc means comparisons after mixed effects models (n=48).

Table 4. Analysis of Serum Corticosterone Levels, Time Spent in Open Arms.

	C (n=12)	CMS (n=12)	CMS+ S (n=12)	S (n=12)	p value
Serum Corticosterone Levels	322.33±154.26	909.17±474.45	400.58±157.68	372.67±169.22	<0.001***
Time Spent in Open Arms	2.37±1.31	2.26±2.54	5.95±6.08	13.12±8.29	<0.001***

C: Control, CMS: Chronic Mild Stress, CMS+S: Chronic Mild Stress+Sertraline, (n=48).

- Immobility time was significantly decreased in the CMS+S group compared to the CMS group ($p<0.001$).

NORT: Analysis of the NORT revealed significant differences in long-term memory performance (Table 6). Specifically, both the discrimination index ($p=0.005$) and the recognition index ($p=0.009$) were significantly impaired in the CMS group compared to the control (C) group. Additionally, the long-term memory recognition index was significantly different between the CMS group and the sertraline-only (S) group ($p=0.05$). Further analysis of the long-term memory discrimination index showed significant differences between the C and CMS groups ($p=0.005$), as well as between the CMS and S groups ($p=0.032$).

Results of gene expression analysis

The expressions of BDNF, NESTIN, NEUN, and NEURITIN genes in hippocampus tissues were assessed and quantified using a one-way analysis of variance (Figure 2).

Assessment of serum corticosterone concentrations

Serum corticosterone levels were evaluated across the groups and are presented in Table 4.

Discussion

A great deal of research is being conducted using the continuous moderate stress paradigm to examine the effects of 5-HT activity in neurons and 5-HT1A autoreceptor functions in laboratory animals subjected to depression. These investigations have demonstrated that the spontaneous activity of 5-HT can exhibit significant variations across different brain areas [21, 22]. SSRIs have been found to promote developmental plasticity through a mechanism that relies on the neurotransmitter 5-HT. The treatment was found to elevate 5-HT levels, thus enhancing neuronal plasticity [23]. 5-HT modulates glutamate transmission in the brain. It can enhance N-methyl-D-aspartate receptor-mediated plasticity. 5-HT associates with the cell adhesion molecule. The cell adhesion molecule is crucial for cellular transformation and adaptability throughout development. 5-HT promotes the synthesis of the polysialylated variant of the neural cell adhesion molecule (PSA-NCAM), which is involved in synapse formation and neuronal reorganisation [23, 24]. According to Malberg et al., the administration of antidepressant drugs resulted in an increase in the number of newly formed cells after 14 and 28 days. A separate investigation demonstrated that 5-HT exerts a beneficial regulatory influence on the generation of neural precursor cells and the viability of recently formed neurons [15]. Research has indicated that stress situations are linked to heightened activity in the HPA axis and higher

Table 5. Summary of the results of the Forced swimming test.

	15th day Mean±SD	30th day Mean±SD	p value
Control			
Swimming (sn)	89.25±47.48	115.92±46.16	0.142
Climbing (sn)	126.92±31.32	126.50±32.85	*0.974*
Immobility (sn)	85.83±67.28	57.83±40.67	0.059
Movement (%)	71.91±22.25	81.27±14.32	*0.064*
CMS			
Swimming (sn)	41.33±20.12	47.25±27.03	*0.742*
Climbing (sn)	89.08±22.14	97.42±31.76	0.522
Immobility (sn)	169.50±29.67	155.75±41.40	*0.346*
Movement (%)	43.55±9.83	48.00±13.71	*0.372*
CMS+S			
Swimming (sn)	37.25±17.28	128.92±85.07	<0.001***
Climbing (sn)	77.92±18.93	99.08±53.56	0.108
Immobility (sn)	184.08±29.23	71.50±55.05	<0.001***
Movement (%)	38.64±9.60	76.07±18.40	<0.001***
Sertraline			
Swimming (sn)	99.67±23.05	137.67±66.77	0.039*
Climbing (sn)	143.33±25.29	84.42±39.79	<0.001***
Immobility (sn)	59.25±29.89	77.50±58.27	0.212
Movement (%)	80.44±10.23	74.08±19.43	*0.203*

CMS: Chronic Mild Stress, CMS+S: Chronic Mild Stress+Sertraline (n=48) (*p<0.05). (**: p<0.01, ***: p<0.001). Tukey adjusted post hoc lsmeans comparisons after mixed effects models

Table 6. New Object Recognition Test results.

	C n = 12	CMS n = 12	CMS+S n = 12	S n = 12	p-value
Recognition index in short-term	0.39±0.40	0.50±0.48	0.61±0.44	0.81±0.32	0.10
Discrimination index in short-term	-0.05±0.71	0.24±0.76	0.39±0.70	0.62±0.63	0.14
Recognition index in long-term	0.74±0.45	0.17±0.39	0.33±0.49	0.66±0.43	0.009
Discrimination index in long-term	0.72±0.44	0.00±0.60	0.33±0.49	0.59±0.42	0.005

(*: p<0.05, **: p<0.01) Tukey comparisons after One-way Anova (n=48).

levels of corticosterone in the bloodstream [25]. Guimaraes et al. contend that chronic stress activates the HPA axis, resulting in modifications to the serotonergic system in the hippocampus. This, in turn, increases the likelihood of developing depression. Our analysis indicated a significant increase in corticosterone levels within the CMS group [26]. In this study, we utilized the OFT to measure locomotor activity, the EPM to assess anxiety, and the FST asses depression. These tests were used to analyze the efficacy of sertraline, an antidepressant belonging to the SSRI group, in rats showing depressive-like behavior induced by the CMS model. NORT was applied to observe changes in episodic memory. To investigate the effectiveness of newly formed neural precursor cells in this change, BDNF, NESTIN, NEUN, and NEURITIN gene expression levels were examined to follow neurol gene formation.

Recent studies suggest that deficits in memory and attention in depression may be linked to inhibitory deficits, specifically the inability to disengage from negative stimuli. Rumination on negative emotions has been involved in development, maintenance, and severity of depression. In depressed individuals, attentional biases towards negative stimuli can interfere with the processing of positive information. This is supported by the evidence that depressed individuals pay more attention to negative stimuli and less attention to positive stimuli. This attentional bias may be due to reduced activity in certain brain regions, including the right ventrolateral prefrontal cortex, right dorsolateral prefrontal cortex, and right superior parietal cortex. This diminished activity may impede the capacity to redirect attention from unfavourable stimuli, resulting in extended exposure to depressed influences [27]. Sertraline treatment has been shown to decrease immobility and increase swimming behavior in experimental animals, supporting its antidepressant-like properties [28]. The evidence demonstrates that the CMS concept induces heightened behavioral pessimism and cognitive deterioration [21]. Mice subjected to four weeks of stress have shown a notable rise in the duration of inactivity in the FST [29]. This study found that rats subjected to

a CMS treatment for four weeks demonstrated a marked increase in immobility duration relative to controls, suggesting a depressive-like condition.This effect persisted for two weeks. Treatment with sertraline (10 mg/kg/day) significantly reduced immobility time in the CMS group. Additionally, both the sertraline-only (S) and CMS+S groups showed increased swimming behavior compared to the other groups. These data validate that SSRIs can successfully alleviate depression-like behaviours and anxiety-inducing effects caused by CMS [21, 7, 1].

The 5-HT system is significant in the development of mood disorders [30]. Changes in 5-HT metabolism contribute to the onset of depression. In their investigation, Santiago et al. [31] discovered that serotonin reuptake inhibitors resulted in an increase in swimming time. The OFT was performed to evaluate the locomotor behaviours of the animals. The animals' velocity, distance moved, movement percentage, and parameters were evaluated in the OFT. At the outset, there were no notable discrepancies among the groups regarding distance travelled, velocity, or movement percentage in the OFT. However, by day 30, all groups showed a decrease in movement time. In the EPM, the sertraline-treated group spent significantly more time in the open arms, indicating reduced anxiety-like behavior. These findings suggest that sertraline may have anxiolytic effects [31]. Analysis of the OFT and EPM did not reveal significant differences in anxiety-like or avoidant behaviors between the control and CMS groups. While the control group exhibited reduced locomotion in the OFT, this may be attributable to individual behavioral variations during the test. EPM, the CMS group treated with sertraline spent significantly more time in the open arms, consistent with the findings of Peng et al., who reported a similar effect of fluoxetine in a rat model of depression. Li et al. [32] noticed notable augmentation in locomotion in both experimental groups following the injection of sertraline.

The NORT assesses short-term recognition memory in rats, capitalizing on their innate preference for novel objects. Rats typically explore objects through tactile and olfactory investigation using their mystacial vibrissae (whiskers). As nocturnal animals, they rely heavily on non-visual sensory input, including olfactory signals transmitted to the somatosensory cortex via the trigeminal nerve. Therefore, the NORT serves as both a visual and a somatosensory test. Successful performance requires intact visual and somatosensory systems; disruption of either would invalidate the assay as a screen for memory-enhancing drugs. Such disruption would be evident in altered exploration times in the second trial, regardless of object novelty [33]. In our study, there was an increase in discrimination and recognition index in short-term memory in the sertralin-treated groups compared to the CMS. There was a significant difference in discrimination index in long-term memory. A significant difference was observed between the treated group and the control group compared to the CMS group. Individuals suffering from depression have an extended duration in the processing of emotional stimuli, which may indicate a potential impairment in their ability to exert cognitive control over the limbic parts of the brain. Reduced activity in these specific brain regions may hinder the capacity of those suffering from depression to control unpleasant and recurrent thoughts. The hippocampus, a key area for episodic memory, enhances the process of encoding and retrieving emotional events in individuals under physiological conditions. Depressed people had heightened activity in the amygdala, hippocampus, caudate, and putamen during the encoding process. This enhanced activity facilitated the recall of negative information while not affect the recall of good information. This discovery indicates that memory bias in individuals with depression may stem from heightened amygdala activity during the process of encoding information, as well as higher activity in the hippocampus, caudate, and putamen while recalling negative information, as compared to individuals without depression. Although the neural circuits underlying the pathology of depression remain unclear, the diverse symptoms of depression suggest that more than one brain region may be responsible. According to previous reports, learning and memory regions were the most affected brain regions after stress [27]. The slowing of neurogenesis, the absence of new neuron formation and the reduction of dendritic branching may be responsible.

Brain-derived neurotrophic factor (BDNF) is a crucial modulator of neuronal viability, synaptic plasticity, and memory development in the central nervous system (CNS). Many antidepressants, including sertraline, have been shown to increase BDNF expression in the brain. While depression is often associated with reduced hippocampal BDNF levels and impaired cognitive function, antidepressants can help restore BDNF and improve cognition This study indicates that the observed elevation in BDNF after sertraline treatment may enhance cognitive abilities [34]. Wang et al. demonstrated that demonstrated that chronic stress negatively affects synaptic connections in the rat hippocampus, causing them to become shorter, thinner, and less efficient. BDNF therapy enhanced dendritic spine density in the CA1, CA3, and dentate gyrus (DG) regions of the hippocampus and decreased the diameter of the synaptic cleft in the CA1 region. These findings highlight the potential of BDNF to counteract the negative effects of stress on synaptic plasticity [35]. Moreover, nestin and doublecortin, indicators of neurogenesis, are frequently present in developing brain progenitor cells during adult neurogenesis [35, 36]. In our research, nestin levels were significantly decreased in rats with depressive behavior. Sertraline restored BDNF expression and up-regulated nestin, indicating that it leads to neurogenesis. Yang et al. [37] demonstrated a notable reduction in BDNF and NeuN levels following CUMS. They also examined NeuN expression using immunofluorescence and demonstrated a reduction in neuronal cells. After 3 weeks of fluoxetine administration, they observed an increase in new neurons. Decreased dendritic spike density and dendritic branching were associated with psychiatric disorders [37]. Our study, decrease in NeuN levels was found in the CMS group. Antidepressant drugs caused an observed increase. Our experimental model showed that it effectively decreased the growth of neural precursors in hippocampus by reducing the number of mature neurons (NeuN). Son et al. [38] showed a decrease in Neuritin levels in the depression group. Our study also shows that prolonged mild stress

leads to a decrease in neuritin levels in the hippocampus. Sertraline administration did not affect neuritin levels.

Our research offers significant insights into the impact of psychological stress on adult hippocampus neurogenesis and the possibilities for therapeutic intervention. Importantly, we expanded the analysis of subacute sertraline administration to two weeks, using a clinically relevant dosing regimen that aligns with potential therapeutic applications. This extended period enabled us to assess both the short- and long-term effects of sertraline on depressive behaviours and neurogenesis. A disadvantage of this study is that only gene expression in hippocampal tissue was examined. Due to budget constraints, protein analysis was not possible. Future studies should include protein-level measurements using techniques like Western blot or immunofluorescence.

Conclusion

Animal models are crucial for understanding the neurobiological mechanisms underlying mood disorders in humans. While the precise neural circuits involved in stress-induced mood and energy balance alterations remain incompletely understood, our study confirms previous findings that chronic stress suppresses hippocampal cell proliferation and neurogenesis. Furthermore, we demonstrate that sertraline effectively alleviates depressive symptoms in this model, as evidenced by behavioral measures [39]. Moreover, this suppression was more pronounced in the ventral hippocampus. Chronic sertraline administration, in accordance with prior findings, mitigated the CMS-induced inhibition of hippocampus cell growth and neurogenesis [40].

Ethical approval

This study protocol was approved by Necmettin Erbakan University Experimental Medicine Application and Research Center Experimental Animals Local Ethics Committee (No: 2021-029).

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