Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp. 669-679.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/

BULL. PHARM. SCI. Assiut Univ.

GABAPENTIN PREVENTED DEPRESSIVE BEHAVIOR INITIATED BY DEXAMETHASONE, STRESS OR INFLAMMATION IN MICE

Azadeh Mesripour[1*], Asiye Salehzade[2], Valiollah Hajhashemi[2]

[1]*Isfahan Pharmaceutical Sciences Research Center, Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran*
[2]*Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran*

Gabapentin, an anticonvulsant drug, used for neuropathic pain, also it has protective effects against psychological stress with a mild side-effect profile. Evidence link high glucocorticoids blood levels and stress to nitric oxide and depression. Thus the aim was to assess the effectiveness of gabapentin in treating depression following dexamethasone (Dex) administration, exposure to stress, and complete Freund's adjuvant (CFA) induced inflammation in mice. Male NMRI mice (weighing 28 ± 2 g) were used. Dex (15 µg/kg, subcutaneously) was administered for 7 days, stress was induced by water avoidance stress (WAS), and CFA was injected into the mouse paw for 17 days. Gabapentin or imipramine (both 10 mg/kg, intraperitonealy) were administered for 7 days. Locomotor activity, the force swim test (FST), sucrose preference (SP) test, and the novelty suppressed feeding (NSFT) were measured. During the FST, immobility time significantly increased by Dex, WAS and CFA compared to the control group. WAS and CFA groups increased latency time and reduced food consumption in NSFT, SP also decrease. Treatment with gabapentin (alike imipramine) along with Dex, stress, or CFA significantly reduced immobility time in FST, and SP increased. During NSFT in stress and CFA groups treated with gabapentin latency time reduced and food consumption increased. There was no significant alteration in the animals' locomotor activity. In conclusion, gabapentin prevented dexamethasone, stress or inflammation-induced depression in mice. Thus it is promising for depression related to these conditions in patients.

Keywords: *Animal experiments, Mental disorder, Alternative medicine, Freund's adjuvant, Nitric oxide*

INTRODUCTION

Studies have identified nitric oxide (NO) signaling as a promising target for the treatment of major depressive disorder (MDD). These studies have reported an upregulation in the enzymes involved in NO production, (NO synthase [NOS]), as well as elevated levels of NO metabolites in individuals experiencing depression[1]. Furthermore, paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been found to have an inhibitory effect on NOS, leading to a decrease in NO levels[2].

NO is a vital messenger molecule in the brain, synthesized by NOS from L-arginine. NO has diverse roles in the central nervous system (CNS) such as neurogenesis, synaptic plasticity, learning, memory, pain perception, and depression[3,4]. Recent evidence showed that blocking NO synthesis prevents stress-induced behavioral alterations in rodents. NO can reduce serotonin levels in the brain, impairing serotonergic transmission and adaption to stress. Inhibiting NO synthesis produces antidepressant-like effects in rats, suggesting its involvement in stress and depression-related processes[5].

Stressful life events play a significant role in the development of MDD[6]. Stress triggers an increase in glucocorticoid (GC) secretion,

Received : 8/1/2024 & Accepted : 19/3/2024

*Corresponding author: Azadeh Mesripour, E-mail: a_mesripour@yahoo.com

which is typically regulated by a negative feedback mechanism in the hypothalamic-pituitary-adrenal axis (HPA) to maintain balance. However, if the stress stimulus exceeds, glucocorticoid secretion can become uncontrolled and harmful. This can result in a range of adverse effects, including mood alterations, anxiety, and cognitive impairment[7]. Animal studies have indicated that administering high doses of the stress hormone corticosterone (an analog of cortisol in humans) or synthetic GCs (such as dexamethasone) can induce depressive behavior in rodents[8,9]. Also the available evidence strongly indicate that prolonged administration of GCs and the consequent hyperactivity of the HPA axis may serve as a potential underlying factor for depression[10].

Hippocampal neuronal NOS (nNOS) plays a vital role in stress-related depression, as nNOS overexpression in response to chronic mild stress and corticosterone is closely associated with depressive behaviors. Emerging research has revealed a correlation between stress-related depressive behaviors induced by glucocorticoids and the overexpression of nNOS in the hippocampus, leading to a reduction in GC receptor levels[11].

Gabapentin (Gab), an anticonvulsant drug, also used in treating neuropathic pain is a structural analog of γ-aminobutyric acid (GABA). Gab has shown benefits for psychiatric disorders, including depression and anxiety, and has a mild side-effect profile[12,13]. Chronic administration of gabapentin, has protective effects against long-term psychological stress consequences, despite its anticonvulsant properties[13]. Gab has been found to inhibit depolarization-induced NOS stimulation by blocking both P/Q-type and L-type Ca2+ channels. It has been suggested that the mechanism of action of Gab may involve modulation of the NO/cyclic guanosine monophosphate (cGMP) signaling pathway[14,15].

The objective of our study was to assess the effectiveness of Gab in treating depression induced by dexamethasone (Dex) administration, exposing animals to stress, and complete Freund's adjuvant (CFA) induced inflammation in mice.

MATERIALS AND METHOD

Chemicals

The chemicals, including Gab hydrochloride, was obtained from Amin Pharmaceutical Company, Iran. The CFA and Imipramine hydrochloride (Imi) was purchased from Sigma-Aldrich, Germany. Dex, in the form of an 8 mg/2 mL ampoule, was sourced from Raha Pharmaceutical Company, Iran.

Animals

The study used male NMRI mice, weighing 28±2 g and aged 6-8 weeks. The mice were housed at a room temperature of 21±2 ºC and a 12-hour light-dark cycle (lights on at 6 AM). They were provided with standard mice chow and access to drinking water. The animals were acclimated to the testing room for 48 hours prior to the experiments. To minimize the impact of time on animal behavior, all tests were conducted between 8 AM and 1 PM in a calm and controlled environment of Pharmacology Department laboratory. Ethical considerations were strictly followed in accordance with the guidelines for the Care and Use of Laboratory Animals issued by National Ethical Committee of Iran (Ethical No IR.MUI.AEC.1401.003, Approval date: 2022-6-27).

Study design

14 groups of mice were studied, with each group consisting of 6 mice. The Gab (10 mg/kg) group intraperitonealy (IP), optimal dose was based on pilot study and a previous study [15], the control group received normal saline (1 ml/100g, IP). Dex group received subcutaneous (SC) injection of Dex (15 μg/kg) [8], the control group received normal saline (1 ml/100g, SC). Gab-Dex group, and Imi-Dex received reference antidepressant Imi (10 mg/kg, IP) and Dex. All the treatments were for 7 days. The locomotor test was conducted, prior to the force swim test (FST) on day 8. Other groups were studied as below.

In order to further evaluate the effect of Gab on depressive behavior two more models of depression were performed by inducing stress, and inflammation by CFA that continued for 14 days. Thus in the following groups in addition to FST that is an acute model for evaluating depression, the novelty

suppressed feeding test (NSFT) was also performed that is a chronic model for evaluating depression[16,17].

Stress was imposed by the water avoidance stress (WAS) model, each mice was placed on a platform located in the center of a Plexiglas apparatus (40×25×20) containing shallow water (22ºc, 3 cm from the bottom), the platform was 1cm above the water. Animals were exposed to stress one hour each day for 14 consecutive days[18]. The stress group of mice practiced WAS, while in the control group animals were each placed in a similar container but without water. Other groups were, WAS-Gab and WAS-Imi group that received Gab or Imi for the last seven days.

In other groups inflammation was induced by CFA (50µl) injection into the right hind paw for 14 days[19]. One group that was only injected with CFA, while the control group received normal saline (50µl) into the right paw. Other groups were, CFA-Gab, and CFA-Imi groups that received treatments for the last seven days.

The locomotor test and FST were performed on day 15. The NSFT was performed on day 16. The sucrose preference (SP) test was conducted during the final three days of each protocol, started from day12.

Locomotor activity

At the beginning of the behavioral experiments, locomotor activity was conducted using a device manufactured by Borj Sanat Company, Iran. The device consisted of a cubic open space with the floor divided into 15 sections by infrared beams. The mice were placed in the chamber facing the wall and allowed to explore the environment for 3 minutes[8,20]. The overall activity of each animal was evaluated by summing the number of section crossing (horizontal movements, automatically counted), and the number of instances of standing on the hind legs (vertical movements manually recorded).

Force swim test

Mice were placed in a 2-liter container with 15 centimeters of water at 23-25 °C and forced to swim. The test lasted for 6 minutes, with the initial 2 minutes for habituation and the remaining 4 minutes for the measuring immobility time using a camera[8]. The immobility time was considered when the animal had only minor movements necessary to keep its head above water, with no active swimming. This state of immobility was considered as a sign of behavioral despair[16]. At the end of the test, the mice were carefully dried to prevent hypothermia and put back to their cage.

Novelty suppressed feeding test

For this test, three pieces of mice chow were weighed and placed in a small dish at the center of a plastic box (40×25×20 cm_3) that was covered with a thin layer of wood shaving. Following an 18 hours of food deprivation, the animal was gently situated in a corner of the box. During the test, the latency until the first encounter with food in the new environment was recorded, alongside the measurement of food consumption after 30 minutes by weighing the leftover chow[17].

Sucrose preference test

This test assessed anhedonia as a phenotype of depression and involved a 3-day procedure. On the initial day, two bottles containing sucrose solution (2.5%) were introduced into the animal's cage. After 24 hours, one of the sucrose bottles was displaced with tap water. Following a habituation period, two bottles containing a specific amount of sucrose solution and water were placed in the cage, and the consumption was measured the day after (SP=sucrose solution intake/ water plus sucrose solution intake ×100). Anhedonia was indicated by a sucrose preference below 65%[21].

Data processing and statistical analysis

The results of all groups were expressed as mean ± SEM. Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparisons test. Statistical significance was defined as $p< 0.05$. The data analysis and making graphs were conducted using the GraphPad Prism 8 and Excel 2020.

RESULTS AND DISCUSSION

Results

The effect of Gab following Dex injection on depressive behavior

As depicted in **Fig.** 1a, after 7-days' treatment with Gab during FST immobility time reduced significantly (131.8 ± 11.3 s vs. 178.9 ± 9.9 s, $p<0.01$). Dex administration significantly increased immobility time compared to the control group (210.8 ± 4.8 s vs. 172.5 ± 7.2 s, $p<0.01$), while the co-administration of Dex-Gab showed a lower immobility time (131.9 ± 5.5 s) than control ($p<0.001$) and Dex alone group ($p<0.001$). The results of SP test confirmed the findings of FST, in Gab group exhibited high SP (75%) where it was 68% in the control group, in Dex SP droped to 51% and in Dex-Gab again it raised up to 70%. The changes in the results induced by Imi were similar to those observed with Gab. As shown in **Table 1** the administration of drugs did not lead to significant changes in the locomotor activity.

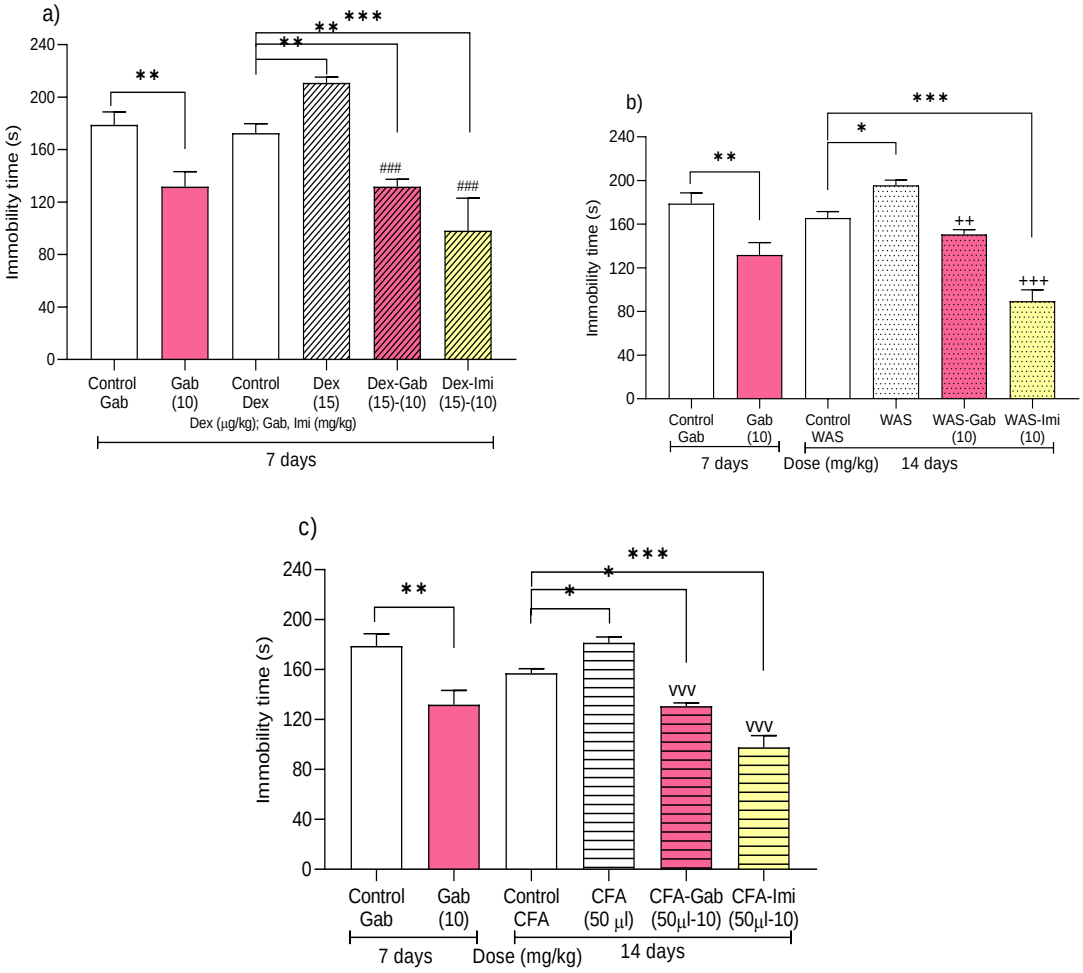

Fig. 1: Effect of gabapentin on immobility time in force swim test following exposure to dexamethasone, stress or inflammation. Immobility time following dexamethasone (Dex) SC injection for 7 days (a), control groups received normal saline, gabapentin (Gab) and control Gab and imipramine (Imi) were injected IP for 7 days. Immobility time after 14 days' baring water avoidance stress (WAS) (b) the control WAS animals were placed in the container without water. Immobility time after inflammation induced by complete Freund's adjuvant (CFA) injected into the right hind paw for 14 days (c) in control CFA group received normal saline. Results are reported as Mean ± SEM (n=6). Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. As the lines show* $p<0.05$, ** $p<0.01$, *** $p<0.001$, ### $p<0.001$ compared to Dex alone, ++ $p<0.01$, +++ $p<0.001$ compared to WAS, vvv $p<0.001$ compared to CFA alone.

The effect of Gab following WAS on depressive behavior

As shown in **Fig. 1b**, WAS for 14 days significantly increased immobility time during FST (195.3 ± 5.1s vs. 165.8± 5.7 s $p<0.05$). However, the administration of Gab from the 7^{th} to 14^{th} day resulted in a significant reduction in immobility time (150.7 ± 4.3 s) compared to WAS group ($p<0.01$). The SP level in WAS group was 54%, while in WAS-Gab it was 72%, which aligned with the results of FST. All these changes occurred without any alteration in the locomotor activity **(Table 1)**.

In NSFT as presented in **Fig.2(a,b)**, there was a significant increase in latency to start feeding in WAS (131.3 ± 4.3s vs 103.0 ± 4.8 s, $p<0.05$), whereas the administration of Gab with WAS significantly reduced the latency (91.17 ± 5.9 s) compared to WAS ($p<0.001$). The amount of food consumed after 30 minutes was significantly lower in WAS (7.4±0.6 mg/g body weight) compared to the control group (10.9±0.4 mg/g body weight). However, this value in WAS-Gab (14.0±0.8 mg/g body weight) showed a significant increase compared to control ($p<0.05$) and WAS ($p<0.001$). The results of the Imi group were similar to those obtained with Gab.

The effect of Gab following CFA practice on depressive behavior

The immobility time during FST is presented in **Fig. 1c**, CFA injection increased immobility time compared to control (181.5 ± 4.6 vs 157.0 ± 3.6 s, $p<0.05$). However, Gab administration from the 7^{th}-14^{th} day reduced immobility time (130.7 ±2.7 s) compared with control ($p<0.05$) and CFA ($p<0.001$). The SP level in CFA was 55%, while in CFA-Gab it was 74%, consistent with FST results. The results showed that there were no significant changes in locomotor activity **(Table 1**).

During NSFT, as shown in **Fig. 2(c,d)**, no significant difference in latency time was observed between the CFA (117.0 ± 9.5 s) and control group (98.3 ± 10.2 s), but CFA-Gab reduced latency time (57.7± 3.1 s) compared to control ($p<0.01$) and CFA ($p<0.001$). There was no difference in food consumption after 30 minutes in CFA (9.1 ± 0.4 mg/g body weight) compared to control (11.7 ± 0.8 mg/g body weight). However, CFA-Gab showed significant increase (15.1 ± 1.1 mg/g body weight) compared to CFA ($p<0.001$). The results in the CFA-Gab group were comparable to those in the CFA-Imi group.

Table 1: Total activity recorded during the locomotor activity test.

Groups (n=6)	Total activity no.	Groups (n=6)	Total activity no.
Control Gab	172.6±11.1	WAS	154.6±14.7
Gab (10 mg/kg)	140.2±14.4	WAS-Gab	189.1±14
Control Dex	158.6±12.6	WAS-Imi	166±15.1
Dex(15 µg/kg)	166±12.6	Control CFA	155.1±16.9
Dex-Gab	161.5±12.4	CFA(50µl)	154±15.5
Dex-Imi	154.5±12.5	CFA-Gab	153.1±12.6
Control WAS	184.2±4.9	CFA-Imi	164±20.2

Total locomotor activity= horizontal movements+vertical movements. Control groups received normal saline (N/S), gabapentin (Gab) and control Gab and imipramine (Imi, 10mg/kg) were injected IP for 7 days. Dexamethasone (Dex) was injected SC for 7 days and control Dex received N/S. Water avoidance stress (WAS) was imposed for 14 days the control WAS animals were placed in the container without water. Inflammation induced by complete Freund's adjuvant (CFA) into the right hind paw for 14 days and control CFA were injected normal saline. Results were reported as Mean ± SEM. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test ($p>0.05$ compared to the related control group).

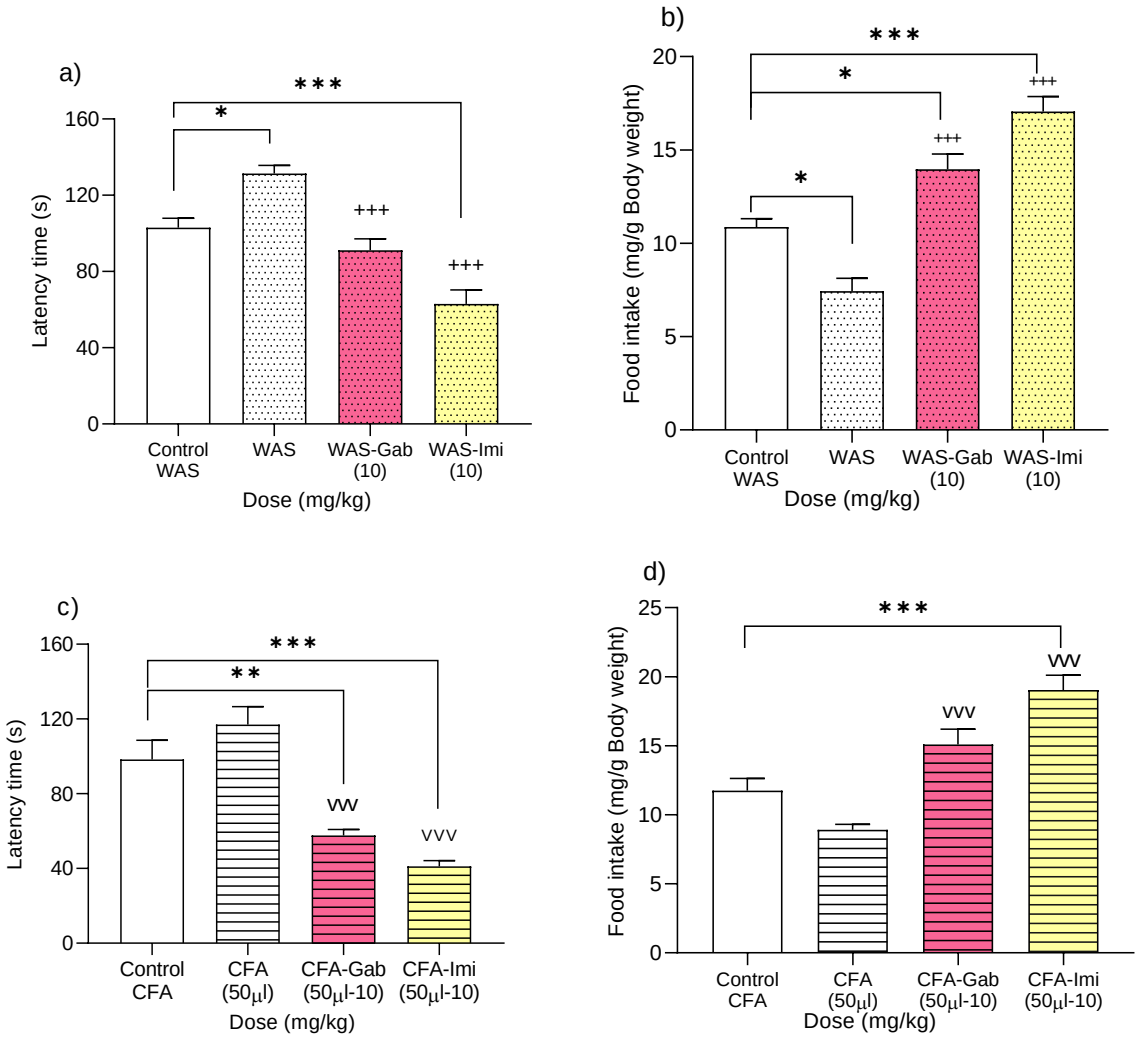

Fig. 2: Effect of gabapentin on novelty suppressed feeding test following exposure to stress or inflammation. Latency (a) and food consumption (b), after14 days' baring water avoidance stress (WAS), the control WAS animals were placed in the container without water. Latency (c) and food consumption (d), after inflammation induced by complete Freund's adjuvant (CFA) injected into the right hind paw for 14 days, control CFA group received normal saline. Gabapentin (Gab) and imipramine (Imi) were injected IP for 7 days. Results are reported as Mean ± SEM (N=6). Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. As the lines show* $p<0.05$, ** $p<0.01$, *** $p<0.001$, +++ $p<0.001$ compared to WAS group, vvv $p<0.001$ compared to CFA.

Discussion

Our study demonstrated the potential antidepressant effects of Gab following depression induced by GC administration or stress and inflammation. The 7-day administration of Gab, resulted in a reduction in immobility time in FST, consistent with previous findings[15,22]. While the locomotor activity results showed no significant alteration in the total activity compared with the control group, therefore results observed during FST were consistent. Additionally, Gab treatment showed a higher percentage in SP, indicating its hedonia effects. The full neurobiological mechanism of Gab has not yet been clearly defined, although it is known that there is no direct action on GABA receptors[23]. The current understanding is that the mechanism of action of Gab involves the suppression of voltage-gated calcium channels that possess the α2δ subunit[24]. A Study have demonstrated that Gab effectively blocks the flow of Ca2+ through L-type, N-type, and P/Q-type calcium channels in rat dorsal root ganglion cells[25]. Furthermore, previous research has indicated the involvement of L-type and P/Q-type calcium

channels in the depolarization-induced NOS activation[26]. These findings imply that the inhibition of P/Q-type and L-type calcium channels might contribute to the central effects of Gab, such as its antiepileptic and neuroprotective properties[14]. In the past two decades, several preclinical studies have indicated that inhibition of NOS can produce antidepressant behavioral effects in various animal models[5,27-29].

Dex administration led to increase in immobility time during the FST. Furthermore, SP decreased, indicating anhedonia in the animals. These results demonstrated that 7-day administration of Dex induced depression in mice. Since, there were insignificant changes after Dex administration in overall activity during the locomotor test, the increase immobility time during FST indicated despair behavior in mice. Previous animal model has demonstrated that Dex administration can induce depressive-like behaviors, which aligns with our findings[7,8,30]. Treatment with Gab was able to reverse these effects, resulting in a decrease in immobility time during FST and an increase in SP in the animals. NO has been identified as a potential mediator between GC and the hippocampal GR. nNOS acts as a suppressor of GR in the hippocampus, suggesting that increased nNOS expression may contribute to chronic stress-induced GR impairment[31]. A signaling cascade has been demonstrated whereby GCs increase the expression of nNOS in the hippocampus via mineralocorticoid receptor (MR) activation. Consequently, this triggers the downregulation of hippocampal GR through both cGMP-dependent and cGMP-independent mechanisms. This alteration results in hyperactivity of the HPA axis, ultimately influencing stress-related depressive behaviors[11].

Exposure of animals to the WAS for 14 days resulted in depression-like symptoms, as indicated by increased immobility time in the FST and decreased SP, these findings were consistent with a previous study[18]. Also in NSFT latency to eat increased and amount of food consumption decreased. Exposure to WAS did not cause any important change in total activity during the locomotor test compared with the control group, thus depressive behavior remained valid. Treatment with Gab starting from the second week was able to reduce immobility time in the FST. In the NSFT, the latency to eat was reduced, indicating a decrease in animal stress, and food consumption increased. The animals also showed a higher preference for consuming sucrose, confirming the antidepressant effect of Gab. Unlike FST the NSFT evaluates depressive behavior following chronic modulations in rodents[32]. Anxiety is induced in animals presented to new environment, that is indicated by hyponeophagia and increased latency. Water avoidance stress is a well-known method acting as a powerful psychological stress inducer, resulting in substantial elevations in adrenocorticotropic hormone and corticosterone levels within 30 minutes[33]. It has been shown that psychological stress generally leads to positive modulation of NOS mRNA expression and increased enzyme activity. The nitrergic system is known to impact various physiological pathways in response to both short- and long-term stress. This can lead to significant neurological damage and the potential development of secondary neurological disorders like depression[34]. Thus Gab could be effective in improving stress related depression that warrants further investigations.

To further evaluate the antidepressant effect of Gab, chronic inflammation was induced by CFA injection, which was able to induce depression-like symptoms in animals. Similar to the findings of the previous study, CFA injection increased immobility time in the FST[35] and decrease the SP percentage. In the NSFT time of latency increased, while reducing the amount of food consumed. While there was no alteration in overall activity during the locomotor test, compared with the control group, depression behavior in mice was confirmed. All these results indicated the induction of depressive-like effects by CFA injection. Administration of Gab starting from the second week was able to reverse the depressive effects and reduce the immobility behavior observed in the FST, demonstrating its antidepressant effect. This was further supported by the SP test and NSFT, where the latency was reduced and the amount of food consumed increased compared to the CFA group. It has been shown that serum levels of NO are significantly increased by CFA-induced

inflammation[36]. In another study, peripheral inflammation caused by CFA increased the expression of nNOS in the dorsal horn of the mouse spinal cord[37]. The positive antidepressant effects observed in rodents treated with NOS inhibitors support the hypothesis that drugs capable of reducing the neurotoxic impact of pro-inflammatory cytokines, NO, and other neurotoxins may have potential as antidepressant treatments[38].

All these methods that induced depression in animal have one mechanism in common, that they all induced NOS. Since Gab administration improved depression induced by (Dex, WAS, or CFA) therefore this research confirms the mechanism of action of Gab involve modulation of the NO/cyclic guanosine monophosphate (cGMP) signaling pathway.

By using rat dorsal root ganglion neurons in a whole-cell patch clamp investigation Sutton et al. (2002) revealed that Gab nonselectively blocks Ca2+ channels[25]. In another similar study the changes of voltage activated Ca2+ channels in dorsal root ganglion neurons of neuropathic rats were assessed following using Gab[39]. Following using Gab in injured neurons, the current reduced, while it was unchanged in adjacent normal neurons. Therefore, the inhibitory effects of Gab might depend on the specific neuropathological situations[39]. According to Oka et al. (2003) the nonselective Ca2+ channels inhibition expressed in primary neuronal culture of mice cerebral cortex is involved in the CNS actions of Gab, including its antidepressant effect. After Ca2+ binds to the calcium–calmodulin complex it is activated and then motivates NO production by NOS[14]. The NO liberated can activate a NO-sensitive guanylyl cyclase that produces cGMP. Three isoforms of NOS are expressed in different areas of the CNS, and nNOS isoform activity is calcium-calmodulin dependent[40].

The findings of this study demonstrated the efficacy of Gab in preventing depression related to glucocorticoids, stress, and inflammation. The potential antidepressant effects of Gab are likely by targeting the central NOS pathway. This conclusion would be supported by further studies exploring the drug's mechanisms of action, comparing its antidepressant efficacy in male and female mice, and to other antidepressant drugs.

Acknowledgement

This work was supported by Isfahan University of Medical Sciences Research Council (Grant No. 3401170, 16/08/2022). authors report no conflicts of interest in regard to this research.

REFERENCES

1. P. Kudlow, D.S. Cha, A.F. Carvalho, and R.S. McIntyre, "Nitric oxide and major depressive disorder: Pathophysiology and treatment implications", ***Curr Mol Med***,16(2), 206-215 (2016)
2. D. Prabhakar, and R. Balon, "How do SSRIs cause sexual dysfunction", ***Curr Psychiatr***, 9(12),30-34 (2010)
3. J.V.Esplugues, "NO as a signaling molecule in the nervous system", ***Br J Pharmacol***, 135(5),1079-1095 (2002)
4. Z. Rezaei, S. Hajizadeh, and Z. Piri, "Biological functions of nitric oxide in the brain and brain stem", ***J Kerman Univ Med Sci,*** 29(6), 568-576 (2022)
5. S.R.L. Joca, and F.S. Guimarães, "Inhibition of neuronal nitric oxide synthase in the rat hippocampus induces antidepressant-like effects", ***Psychopharmacology (Berl),***185(3), 298–305 (2006)
6. D.S. Charney, and H.K. Manji, "Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention", ***Sci STKE***, 2004(225), re5 (2004)
7. Papadopoulou, T. Siamatras, R. Delgado-Morales, N.D. Amin, V. Shukla, Y.L. Zheng, *et al.*, "Acute and chronic stress differentially regulate cyclin-dependent kinase 5 in mouse brain: implications to glucocorticoid actions and major depression", ***Transl Psychiatry***, 5(6), e578 (2015)
8. A. Mesripour, F. Alhimma, and V. Hajhashemi, "The effect of vitamin B6 on dexamethasone-induced depression in mice model of despair", ***Nutr Neurosci***, 22(10), 744-749 (2019).
9. D.N. Strelow, L.S. Magalhães, M.P. Paim, L.D. Krüger, J.S. Neto, C.A. Brüning, *et al.*, "Depressive-like behavior and cognitive impairment induced by acute

administration of dexamethasone: Pharmacological effects of 2-phenyl-3-(phenylselanyl) benzofuran in female Swiss mice", ***Prog Neuropsychopharmacol Biol Psychiatry***, 125,110772 (2023).
10. A.Anacker, P.A. Zunszain, L.A. Carvalho, and C.M. Pariante, "The glucocorticoid receptor: Pivot of depression and of antidepressant treatment?", ***Psychoneuroendocrinology***, 36(3), 415-425 (2011).
11. Q.G. Zhou, L.J. Zhu, C. Chen, H.Y. Wu, C.X. Luo, L.Chang L, *et al.*, "Hippocampal neuronal nitric oxide synthase mediates the stress-related depressive behaviors of glucocorticoids by downregulating glucocorticoid receptor", ***J Neurosci***, 31(21), 7579-7590 (2011)
12. M. Fava, "New approaches to the treatment of refractory depression", ***J Clin Psychiatry***, 61(1), 26-32 (2000).
13. S. Ahmed, R. Bachu, P. Kotapati, M. Adnan, R. Ahmed, U. Farooq, *et al.*, "Use of gabapentin in the treatment of substance use and psychiatric disorders: a systematic review", ***Front Psychiatry,*** 10, 228 (2019).
14. M. Oka, Y. Itoh, M. Wada, A. Yamamoto, and T. Fujita, "Gabapentin blocks L-type and P/Q-type Ca 2+ channels involved in depolarization-stimulated nitric oxide synthase activity in primary cultures of neurons from mouse cerebral cortex", ***Pharm Res***, 20(6), 897-899 (2003).
15. S. Ostadhadi, N. Kordjazy, A. Haj-Mirzaian, S. Ameli, G. Akhlaghipour, and A. Dehpour, "Involvement of NO/cGMP pathway in the antidepressant-like effect of gabapentin in mouse forced swimming test", ***Naunyn Schmiedebergs Arch Pharmacol***, 389(4),393-402 (2016).
16. J. C. Strickland, "Guide to research techniques in neuroscience", ***J Undergrad Neurosci Educ***,13(1), R1–2 (2014).
17. A. Mesripour, and T. Ahmadi, "Depression-like effects of levetiracetam was halted by pretreatment with n-methyl-d-aspartate receptor (NMDAR) blockers in mice", ***Bull Pharm Sci Assiut Univ***,46(1), 517-527 (2023).
18. A.Mesripour, and P. Rakhshankhah, "A synbiotic mixture ameliorates depressive behavior induced by dexamethasone or water avoidance stress in a mouse model", ***Turk J Pharm Sci***,18(1), 21-27 (2021).
19. S. Nasr, J. Varshosaz, and V. Hajhashemi, "Ortho-vanillin nanoparticle-doped glucan microspheres exacerbate the anti-arthritic effects of methotrexate in adjuvant-induced arthritis in rats", ***Pharmacol Rep***, 72(3), 680-691 (2020).
20. A. Mesripour, M. Golbidi, and V. Hajhashemi, "Dextromethorphan improved cyclosporine-induced depression in mice model of despair", ***Res Pharm Sci***,15(5), 447-453 (2020).
21. J.P Berrio, and O. Kalliokoski, "Rethinking data treatment: The sucrose preference threshold for anhedonia in stress-induced rat models of depression", ***J Neurosci Methods***, 15, 395, 109910 (2023).
22. F.S. Kilic, S. Ismailoglu, B. Kaygisiz, and S. Oner, "Effects of single and combined gabapentin use in elevated plus maze and forced swimming tests", ***Acta Neuropsychiatr***, 26(5), 307-314 (2014).
23. N.A. De Martinis, J. Kamath, and A. Winokur, "New approaches for the treatment of sleep disorder", ***Adv Pharmacol***, 57(08), 187–235 (2009).
24. G.J. Sills, "The mechanisms of action of gabapentin and pregabalin", ***Curr Opin Pharmacol***, 6(1), 108-113 (2006).
25. K.G. Sutton, D.J. Martin, R.D. Pinnock, K. Lee, and R.H. Scott, "Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurons", ***Br J Pharmacol***, 257–265 (2002).
26. M. Oka, Y. Itoh, and Y Ukai, "Involvement of Na+ and Ca2+ channel activation and resultant nitric oxide synthesis in glutamate-mediated hypoxic injury in rat cerebrocortical slices", ***Life Sci***, 67(19), 2331-2343 (2000).
27. G. Wegener, and V. Volke, "Nitric oxide synthase inhibitors as antidepressants", ***Pharmaceuticals (Basel),*** 3(1), 273–299 (2010).
28. F. Yildiz, B.F. Erden, G. Ulak, T. Utkan, and N. Gacar, "Antidepressant-like effect

of 7-nitroindazole in the forced swimming test in rats", ***Psychopharmacology (Berl)***, 149(1), 41–44 (2000).
29. I.L. Heiberg, G. Wegener, and R. Rosenberg, "Reduction of cGMP and nitric oxide has antidepressant-like effects in the forced swimming test in rats", ***Behav Brain Res***,134(1-2), 479-484 (2002).
30. A.Wróbel, A. Serefko, P. Wlaź, and E. Poleszak, "The depressogenic like effect of acute and chronic treatment with dexamethasone and its influence on the activity of antidepressant drugs in the forced swim test in adult mice", ***Prog Neuropsychopharmacol Biol Psychiatry***, 54, 243–248 (2014).
31. M.Y. Liu, L.J. Zhu, and Q.G. Zhou, "Neuronal nitric oxide synthase is an endogenous negative regulator of glucocorticoid receptor in the hippocampus", ***Neurol Sci***, 34(7), 1167–1172 (2013).
32. S.C. Dulawa, and R. Hen, "Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test", ***Neurosci Biobehav Rev***, 29(4-5), 771-783 (2005).
33. S. Bradesi, I. Schwetz, H.S. Ennes, C.M.R. Lamy, G. Ohning, M. Fanselow, *et al*., "Repeated exposure to water avoidance stress in rats: A new model for sustained visceral hyperalgesia", ***Am J Physiol Gastrointest Liver Physiol,*** 289(1), G42-G53 (2005).
34. A. Kumar, and P. Chanana, Role of nitric oxide in stress-induced anxiety: from pathophysiology to therapeutic target, ***Vitam Horm,*** 103,147-167 (2017).
35. D.J. Burek, N. Massaly, H.J. Yoon, M. Doering, and J.A. Morón, Behavioral outcomes of complete Freund adjuvant-induced inflammatory pain in the rodent hind paw: A systematic review and meta-Analysis, ***Pain***,163(5), 809–819 (2022).
36. C.L. Zheng, K. Ohki, M. Aslam Hossain, A. Kukita, T. Satoh, and O. Kohashi, "Complete Freund's adjuvant promotes the increases of IFN-γ and nitric oxide in suppressing chronic arthritis induced by pristine", ***Inflammation***, 27(4), 247–255 (2003).
37. Y.C. Chu, Y. Guan, J. Skinner, S.N. Raja, R.A. Johns, and Y.X. Tao, Effect of genetic knockout or pharmacologic inhibition of neuronal nitric oxide synthase on complete Freund's adjuvant-induced persistent pain, ***Pain***, 119(1–3),113–123 (2005).
38. B.E. Leonard, Inflammation and depression: A causal or coincidental link to the pathophysiology? ***Acta Neuropsychiatr***, 30(1),1–16 (2018).
39. M. Zhu, X. Sun, X. Chen, H. Xiao, M. Duan and J. Xu, "Impact of gabapentin on neuronal high voltage-activated Ca2+ channel properties of injured-side axotomized and adjacent uninjured dorsal root ganglions in a rat model of spinal nerve ligation", ***Exp Ther Med***, 13(3), 851-860 (2017).
40. R.G. Knowles and S. Moncada, "Nitric oxide synthases in mammals", ***Biochem J***, 298(Pt2), 249–258 (1994).

Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp. 669-679.

نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

جابابنتين حال دون السلوك الاكتئابي الذي بدأه الديكساميثازون أو الإجهاد أو الالتهاب في الفئران

أزاده مصري بور[1*] – آسيا صالح زاده [2] – ولي الله حاجهاشمي [2]

[1] مركز أبحاث العلوم الصيدلانية في أصفهان، قسم الصيدلة وعلم السموم، كلية الصيدلة والعلوم الصيدلانية، جامعة أصفهان للعلوم الطبية، أصفهان، إيران

[2] قسم الصيدلة وعلم السموم، كلية الصيدلة والعلوم الصيدلانية، جامعة أصفهان للعلوم الطبية، أصفهان، إيران

غابابنتين، وهو دواء مضاد للتشنجات، يستخدم لعلاج آلام الأعصاب، كما أن له تأثيرات وقائية ضد الضغط النفسي مع آثار جانبية طفيفة. و قد ربطت الأدلة العلمية ارتفاع مستويات الجلوكورتيكويد في الدم، والإجهاد بأكسيد النيتريك والاكتئاب. وبالتالي، كان الهدف من هذه الدراسة هو تقييم فعالية الجابابنتين في علاج الاكتئاب بعد تناول الديكساميثازون (Dex)، والتعرض للإجهاد (الضغوط)، والالتهاب الناجم عن مساعد فرويند الكامل (CFA) في الفئران.

تم استخدام سلالة فئران NMRI الذكور ذات الاوزان ٢٨ ± ٢ جرام. و قد تم حقن الديكساميثازون (١٥ ميكروجرام/كجم، تحت الجلد) لمدة سبعة أيام، كما تم احداث الإجهاد (الضغط النفسى) عن طريق تجنب الإجهاد المائى، كذلك تم حقن مساعد فرويند الكامل في مخلب الفأر لمدة ١٧ يومًا. فى حين تم إعطاء جابابنتين أو إيميبرامين فى التجويف البريتونى (كلاهما فى جرعة ١٠ ملليجرام / كجم) لمدة ٧ أيام. تم قياس النشاط الحركي، كما تم إجراء اختبار السباحة القسرى (FST)، واختبار تفضيل السكروز (SP)، واختبار إعاقة التغذية الناجمة عن الحداثة (NSFT).

خلال اختبار السباحة القسرى، زاد وقت الجمود (توقف الحركة) بشكل ملحوظ بسبب الديكساميثازون، الإجهاد (الضغط النفسى) و مساعد فرويند الكامل، و ذلك مقارنة بالمجموعة الضابطة. كذلك زاد وقت الكمون و انخفض استهلاك الغذاء في اختبار إعاقة التغذية الناجمة عن الحداثة، فى مجموعة الإجهاد المائى و المجموعة المحقونة مساعد فرويند الكامل، كما انخفض تفضيل السكروز أيضًا فى هاتين المجموعتين. وعلى النقيض، أدى العلاج باستخدام جابابنتين (و إيميبرامين على حد سواء)، جنبا إلى جنب مع الديكساميثازون، الإجهاد (الضغط النفسى) و مساعد فرويند الكامل، إلى تقليل وقت توقف الحركة بشكل ملحوظ في اختبار السباحة القسرى، و كذلك زيادة تفضيل السكروز.بالاضافة إلى ذلك، أظهرت نتائج اختبار إعاقة التغذية الناجمة عن الحداثة في مجموعتى الإجهاد و المجموعة المحقونة مساعد فرويند الكامل، و التي عولجت بالجابابنتين، إلى انخفاض زمن الكمون، و زيادة معدل استهلاك الغذاء، فى حين أن النتائج أوضحت أنه لم يكن هناك تغيير كبير في النشاط الحركي للحيوانات.