

Effect of Sodium Butyrate and Desvenlafaxine on Stress Induced Depression in Rats

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Abstract:

Background: Major depressive disorder is a mental disorder characterized by at least two weeks of pervasive low mood, loss of interest in normally enjoyable activities, desvenlafaxine is one of the most commonly antidepressants, sodium butyrate is a HDACi, which has recently been shown to improve the prognosis in depressed patients. **Purpose:** 1) Assessment therapeutic benefits of sodium butyrate both alone or in combination with desvenlafaxine in a model of stress induced depression. This study included the parameters latency time to achieve immobilization after tail suspension, exploratory behavior on open field, Stereotypic behavior. 2) Assessment of possible side effects of tested drugs both alone or in-combination .The parameters used for this purpose were: histopathological study of heart as a measure of cardiovascular side effects of tested drugs. 3) Identifying the target gene for tested drug (gene expression of serotonin transporter was estimated). **Materials & Methods:** Rats were classified into: Group I: control normal group. Group II: (depression induced rats), Subgroup IIa (non –treated stress induced depressed rats), Subgroup IIb: (sodium butyrate treated group), Group II c: (Desvenlafaxine treated group), Group II d: Both sodium butyrate and desvenlafaxine was administrated. **Results:** Treated groups showed significant improvement in all parameters and improvement of the histopathology of the myocardium at the end of the 3rd week of drug administration. **Conclusion:** it was found that desvenlafaxine or sodium butyrate has anti-depressant effect, with decrease effect with combination.

Key words: depression, serotonin transporter, sodium butyrate, desvenlafaxine, rat behavior.

Abbreviations: HDACi : histone deacetylase inhibitors.

Introduction:

Major depressive disorder is a mental disorder characterized by at least two weeks of pervasive low mood. Low self-esteem, loss of interest in normally enjoyable activities, low energy, neuroathenia in the form of extreme fatigue, muscle aches, somatic discomfort and disturbance of sleep or appetite (1). In 2017 the worldwide lifetime prevalence of major depressive disorders ranged from 2 to 21%, with the highest rates found in some European countries and the lowest in some Asian countries (2). 10-15% of mild and moderate major depressive episodes often resolve over time whether or not they are treated (3). Nevertheless, severely depressed individuals have a shorter life expectancy than those without depression, in part because people who are depressed are at risk of dying of suicide (4).

Sodium butyrate is one of a (HDACis) which are important regulators of synaptic formation, synaptic plasticity, and long-term memory formation (5). The HDACi seem promising for several psychiatric disorders.

Desvenlafaxine is an SNRI with selective inhibitory activity of neurotransmitter uptake at the human serotonin and norepinephrine monoamine transporters (6).

Materials and methods:

This is a controlled clinical trial study conducted during the period from 1/8/2020 to 2/9/2020.

Animals:

Thirty-six adult male albino rats obtained from (Experimental Animal Breeding Farm, Helwan-Cairo) weighing between 150- 200 g were used for in-vivo experiments. They were acclimatized for one week and were caged (8 rat/ cage) in fully ventilated room at room temperature in the pharmacology department, Benha Faculty of Medicine. Rats were fed a standard chow with water.

This study was approved from ethical committee of Benha Faculty of Medicine.

Drugs:

Desvenlafaxine (obtained from Sigma in powder form). Sodium butyrate (obtained from Sigma in powder form). The biochemical analysis was performed using standard kits. The chemicals used in this study were all of high analytical grade.

Experimental groups and procedures:

After one week of acclimatization, tested animals will be divided into 2 groups: **(GI)** (normal control group): comprising 6

animals, **(GII)**: (depression induced rats) comprising 30 rats. Depression was induced by repeated stressful stimuli by immersion in cold water (4°C for 15 minutes /day) and tail suspension for 5 minutes /day) (7). They were monitored for signs of depression namely immobility after tail suspension and on forced swimming, loss of exploratory locomotor behavior on open field every day.

24 rats which showed clear signs of depression were only enrolled in the experiment and divided into 3 subgroups each of them comprised 6 animals, **(Sub G IIa)** (non –treated stress induced depressed rats). After induction of depression, previously mentioned depressive stressful stimuli and monitoring tests were resumed for 3 weeks with no drug treatment, **(Sub G IIb)**: (sodium butyrate treated stress induced depressed rats); they were subjected to stressful stimuli and monitoring tests in similar way to that of group IIa.

Sodium butyrate was administrated in a dose of 200 mg /kg by oral gavage for 3 weeks (8). **(Sub GII c)**: (Desvenlafaxine treated stress induced depressed rats); they were subjected to stressful stimuli and monitoring tests in similar way to that of group IIa. Desvenlafaxine was administrated in a dose of 50 mg /kg by oral gavage for 3 weeks (9).

(Sub GII d): They were subjected to stressful stimuli and monitoring tests in similar way to that of group IIa. Both sodium butyrate and desvenlafaxine was administrated in the same doses as group IIb & IIc.

During experimental period, all animals will be subjected to the same observations as group GII

At 8 am the morning of 21th day of the experiment, animals were evaluated for mood using previously mentioned tests for the last time. They were anesthetized with ether and sacrificed by decapitation. They were rapidly dissected for brain and heart. Hippocampus of each animal were dissected on cold metallic tray and rapidly kept in - 80°C for future use in determination gene expression of serotonin transporter. Heart of all animals were washed in cold water and dried by two filter papers. they were divided longitudinally into two halves and kept on 10% formaldehyde solution and used for histopathological study.

Forced swimming test:

The rats were forced to swim in cold (4°C) water for 3 min. The rats were allowed to swim in a container 15 cm in diameter and 20 cm tall with water filled to a depth of 11 cm. After swimming, the rats were gently

dried, the average time of (immobility) / second was considered an index for depressive stressful behavior (10).

Tail suspension test:

The average duration of (mobility) within the total observation time (2 minutes) was recorded after 7, 14 and 21 days of drug administration compared with normal and non-treated stressful rats, it was considered as index of degree of depression (11).

Open field test:

Allow the rats to acclimate to the procedure room for 30 min before the test, remove a single rat by grasping its tail and place it in the middle of the open field maze, recording using mobile camera, Allow free movement of the rat throughout the maze for a single 3 min period, at the end of the test, pick up the rat gently and return it to its cage (12).

The behaviors scored included: Frequency of central square crossing, Latency, Number of line crossing, rearing (13). In this work, the test was performed after 7 and 14 days of drug administration in comparison with normal and non-treated stress induced rats.

Stereotypic behavior in rats:

A score was constructed to measure the locomotor behavior quoted from (14): 0: asleep, 1: awake but inactive, 2: Active

moving around, 3: Circling: Running around the cage in circles, 4: Stereotypic behavior: spinning around longitudinal body axis, jumping and biting cage bars, backward flip from one cage wall moving along the same route on the cage lid with all four legs, The total observation time is 4 hours after induction of stress. The observation was repeated after 7, 14 and 21 days after drug administration compared with normal and non-treated stress induced depression.

Gene expression of serotonin transporter by real-time PCR:

It was performed using reverse transcriptase: real-time polymerase chain reaction (PCR): Total RNA from hippocampus of all tested animals was extracted by gridding and homogenization in lysis buffer followed by vortex stirring and homogenization in chloroform solution using easy-BLUE™ reagent kit . mRNA was extracted from upper aqueous phase of previous solution using solid phase extraction technique using silica containing spin column.

mRNA of serotonin transporter was extracted using TOPscript™ Reverse Transcriptase kit using 5`-TCG CCT CCT ACT ACA ACA CC-3` sequence as forward primer and 5`- ATG TTG TCC

TGG GCG AAG TA-3` sequence as reverse primer. It was amplified using ABI SDS software (ABI 7900) PCR apparatus against (M. GAPDH) which acted as reference gene (15). Fold expression changes are calculated using the equation

$$2^{-\Delta\Delta CT} \text{ and expressed as relative units (RU) (16).}$$

Histopathological changes:

Ventricles will be separated and preserved in 10% formalin until used for preparing transverse sections. The obtained sections were collected on glass slides, deparaffinized and stained by hematoxylin and eosin stain for histopathological examination through the light microscope (17).

Statistical analysis:

Data are presented as mean (M) \pm SEM and statistically analyzed by

One way ANOVA to determine the overall significance between all groups followed by student t test for measuring the significance between individual groups. Chi square rout and z test were used to test significance when standard error of the mean is invalid (over 10% of the mean (18)).Calculation were performed using Graph Pad Prism 4 software.

Results:

Behavior changes manifested by significant decrease active struggle after tail suspension **figure (2)**, and increase immobility in forced swimming test **figure (1)**. In addition, the exploratory behavior in open field was manifested by increased latency period to start movement, reduced frequency of line crossing and central square entry **figure (3)**. The locomotor behavior score was also markedly decreased **figure (4)**.

Treatment with desvenlafaxine resulted in antidepressant effect manifested by marked increase in duration of active struggle after tail suspension and decrease in duration of negative behavior after forced swimming compared with non-treated stressful rats **figure (1& 2)**. Such values were still worse than normal for the former but normalized in the latter. All components of exploratory behavior in open field, locomotor behavior were improved **figure (3)**.

Sodium butyrate partially improved all tested parameters of depressive, exploratory, locomotor behavior. It had less profound antidepressant effect than desvenlafaxine **figure (1, 2, 3 &4)**

Combination of desvenlafaxine and sodium butyrate exerted marked negative impact on all tested behavioral tests. They were significantly improved compared with non-

treated and sodium butyrate treated animals but markedly worse than desvenlafaxine treated animals except for exploratory behavior on open field which was markedly exaggerated more than normal **figure (1, 2, 3 & 4).**

The behavioral changes induced by stress and tested drugs were associated with changes in gene expression of serotonin transporter which was markedly increased in non-treated stressed animals and significantly decreased in treated animals in correspondence with their observed antidepressant effect **figure (5).**

cardiotoxicity in the form of congestion, hemorrhage and interstitial edema **figure (7).**

Desvenlafaxine partially improved all microscopic abnormalities in stress induced rats compared with non-treated stress induced rats but sodium butyrate exerted marked but weaker effect than desvenlafaxine, while sodium butyrate and desvenlafaxine combination more potent compared with sodium butyrate but weaker than desvenlafaxine **figure(8, 9 & 10).**

Induction of stress by the adopted model in this work, produced a profound

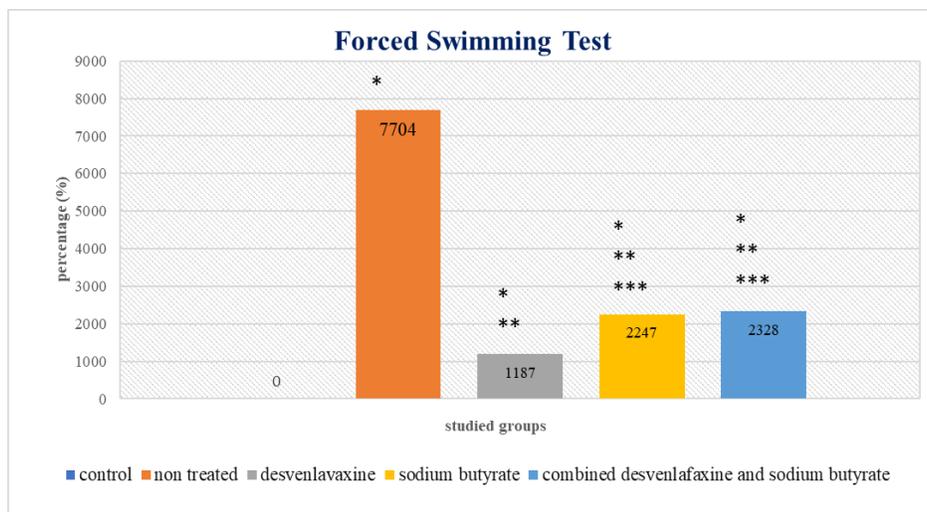


Fig. (1): Bar chart describe effect of desvenlafaxine (30mg /kg/day oral) and sodium butyrate (200 mg /kg/day oral) for 3 weeks either singly or in combination on response of stress induced male albino rats to forced swimming test within total 4 minutes after drug administration representing by percentage change of time of immobility (seconds) after 7, 14 and 21 days (n=6) compared to normal.

*Significant compared with normal control at $p < 0.05$

** Significant compared with non-treated stress induced depressive group at $p < 0.05$

*** Significant compared with desvenlafaxine treated stress induced depressive group at $p < 0.05$

** *Significant compared with sodium butyrate treated stress induced depressive group at $p < 0.05$

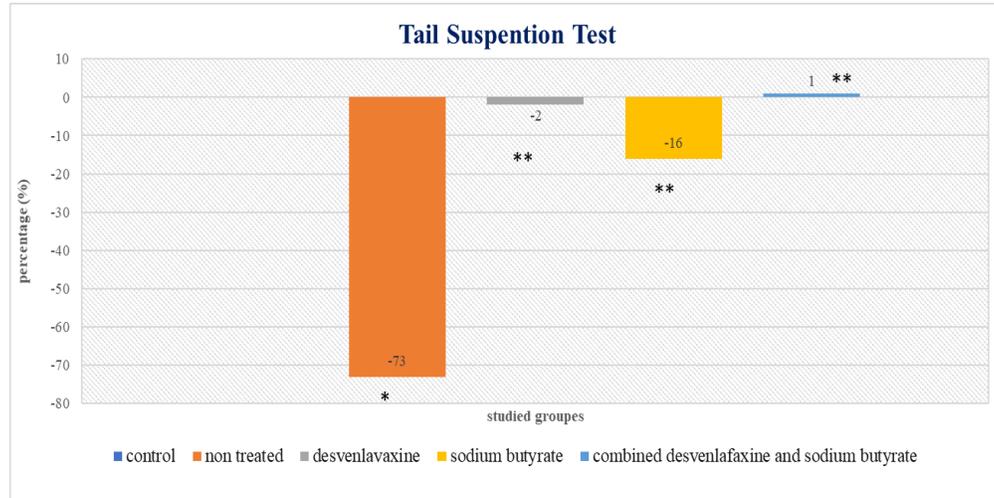


Fig. (2): Bar chart describe effect of desvenlafaxine (30mg /kg/day oral) and sodium butyrate (200 mg /kg/day oral) for 3 weeks either singly or in combination on response of stress induced male albino rats to rat tail suspension within 2 minutes after drug administration representing by percentage change (n=6) of (time of active struggle) compared to normal.

*Significant compared with normal control at $p < 0.05$

** Significant compared with non-treated stress induced depressive group at $p < 0.05$

*** Significant compared with desvenlafaxine treated stress induced depressive group at $p < 0.05$

** *Significant compared with sodium butyrate treated stress induced depressive group at $p < 0.05$

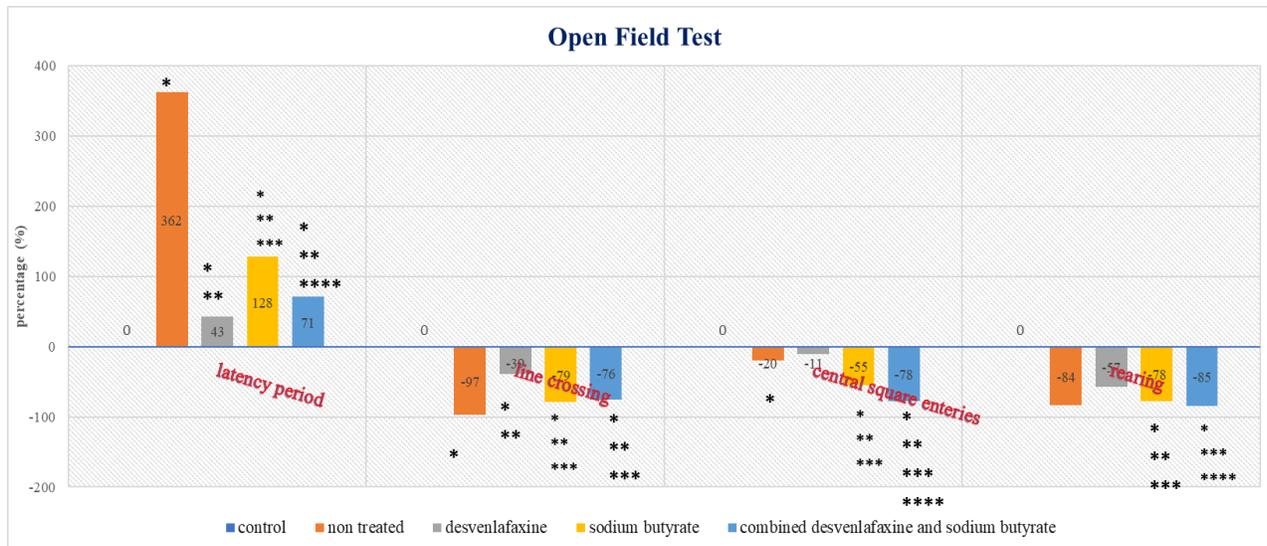


Fig. (3): Bar chart describe effect of desvenlafaxine (30mg /kg/day oral) and sodium butyrate (200 mg /kg/day oral) for 3 weeks either singly or in combination on response of stress induced male albino rats to open field test within minutes after drug administration representing by percentage compared to normal control.

*Significant compared with normal control at $p < 0.05$

** Significant compared with non-treated stress induced depressive group at $p < 0.05$

*** Significant compared with desvenlafaxine treated stress induced depressive group at $p < 0.05$

** **Significant compared with sodium butyrate treated stress induced depressive group at $p < 0.05$

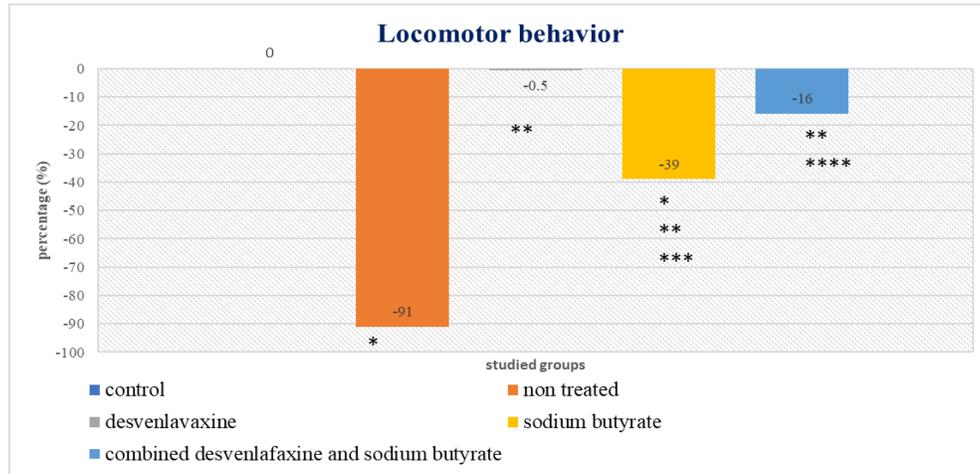


Fig. (4): Bar chart describe effect of desvenlafaxine (30mg /kg/day oral) and sodium butyrate (200 mg /kg/day oral) for 3 weeks either singly or in combination percentage of score of locomotor behavior in stress (forced swimming on cold water)induced depression in male albino rats compared to normal control after 30 minutes of drug administration (n=6).

*Significant compared with normal control at $p < 0.05$

** Significant compared with non-treated stress induced depressive group at $p < 0.05$

*** Significant compared with desvenlafaxine treated stress induced depressive group at $p < 0.05$

** **Significant compared with sodium butyrate treated stress induced depressive group at $p < 0.05$

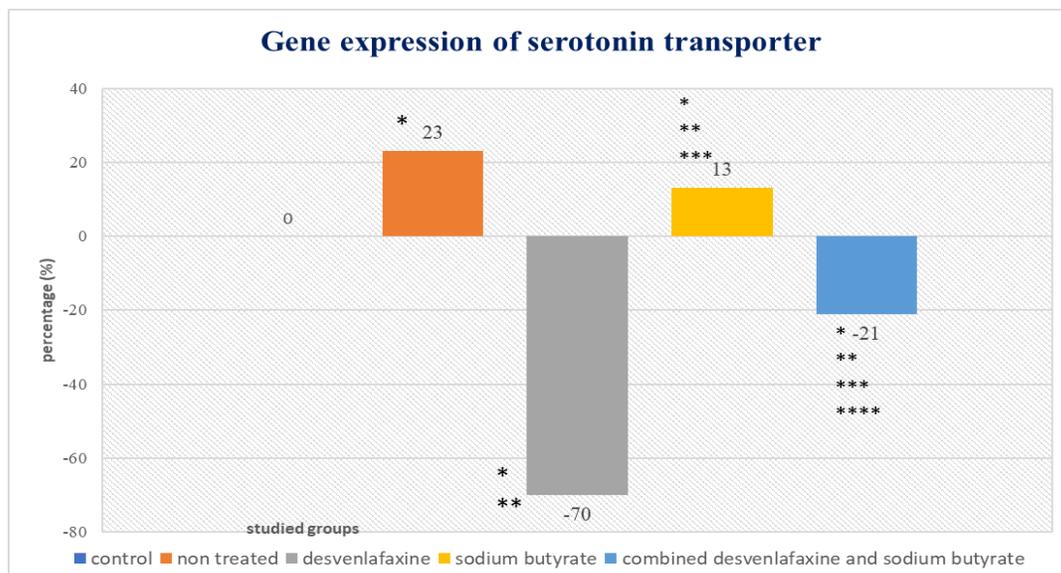


Fig. (5): Bar chart describe effect of desvenlafaxine (30mg /kg/day oral) and sodium butyrate (200 mg /kg/day oral) for 3 weeks either singly or in combination on relative gene expression of serotonin transporter gene represented by percentage change compared to normal control.

*Significant compared with normal control at $p < 0.05$

** Significant compared with non-treated stress induced depressive group at $p < 0.05$

*** Significant compared with desvenlafaxine treated stress induced depressive group at $p < 0.05$

** **Significant compared with sodium butyrate treated stress induced depressive group at $p < 0.05$

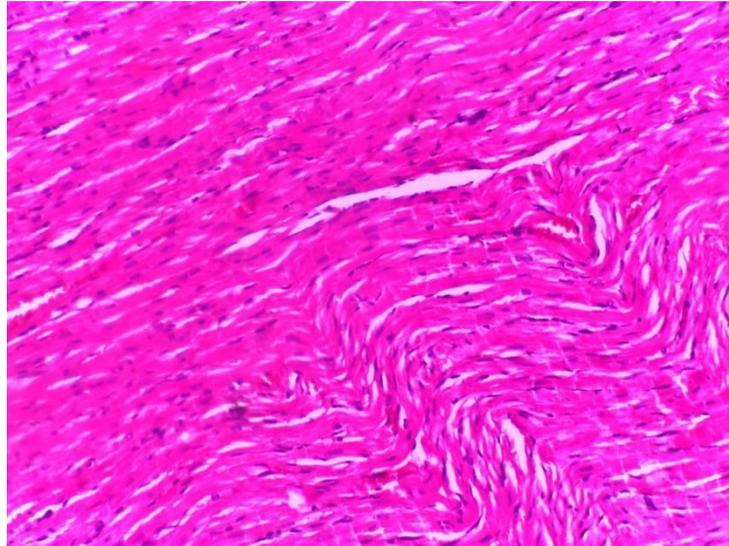


Fig. (6) Photomicrographs of heart sections from normal control rats (H&E) x 200: normal histological structure of the myocardium.

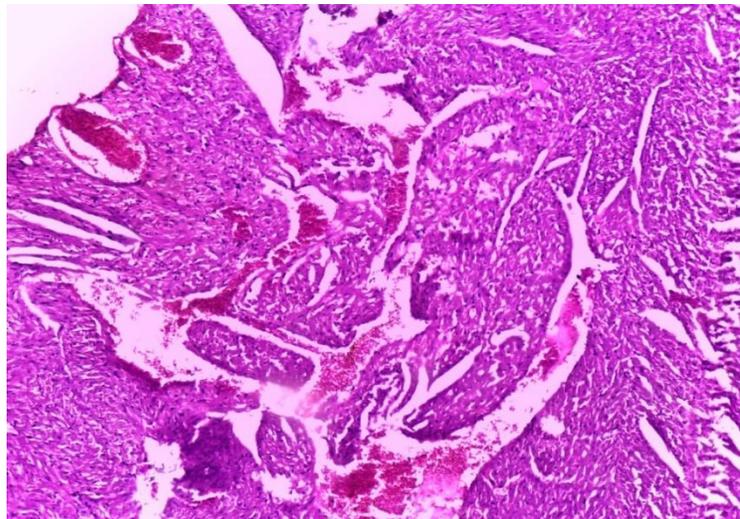


Figure (7) Photomicrographs of heart sections from non-treated rats (H&E) x 200: show hemorrhage, inflammatory cells infiltration and vascular congestion.

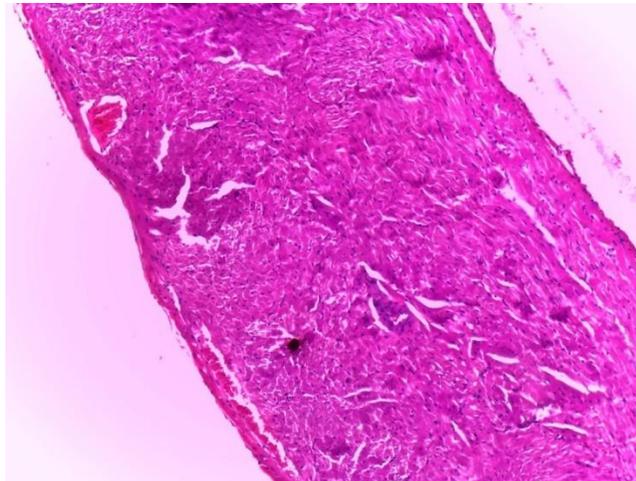


Figure (8) Photomicrographs of heart sections from sodium butyrate treated rats (H&E) x 100: show improvement of (hemorrhage, inflammatory cells infiltration and vascular congestion).

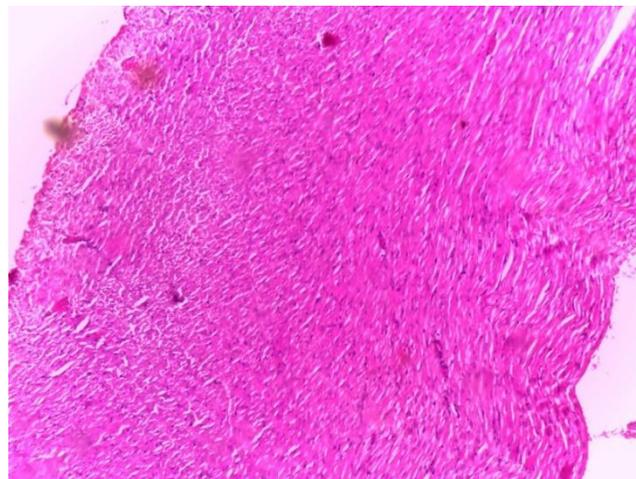


Fig (9) Photomicrographs of heart sections from desvenlafaxine treated rats (H&E) x 100: show improvement of (hemorrhage, inflammatory cells infiltration and vascular congestion).

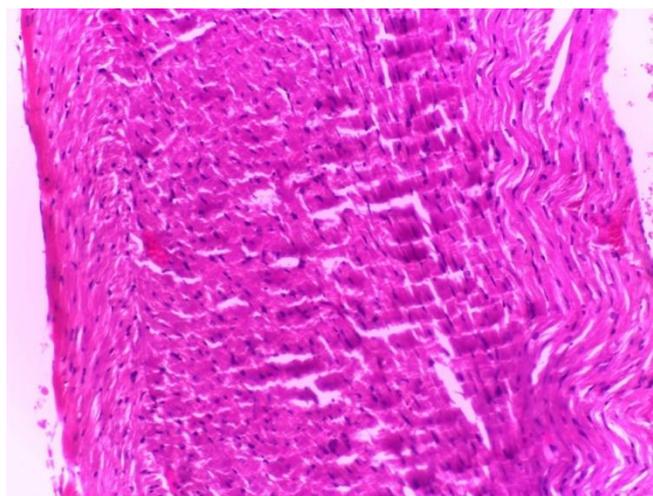


Fig (10) Photomicrographs of heart sections from combined sodium butyrate and desvenlafaxine treated rats (H&E) x 100: show improvement of (hemorrhage, inflammatory cells infiltration and vascular congestion).

Discussion

In this work, a model of depression combining forced swimming, tail suspension and exposure to cold. It is produced rapid and long depression like manifestations in the form of immobility after forced swimming and tail suspension (19). This combined model which started after 7 days and continued for 21 days differs from other researchers that use one model which caused only acute stress (20&21). This was associated with increase expression of serotonin transporter in hippocampus. The latter is a type of monoamine transporter protein that transports serotonin and sodium from the synaptic cleft back to the presynaptic neuron. Thus, it terminates the effects of serotonin on postsynaptic receptors (22). This is in conformation with other researchers (23) who proposed that serotonin released from raphe nucleus in the brain stem elevates mood through promotion of neurogenesis of emotional centers in amygdala, hippocampus and median prefrontal cortex either directly through stimulation of post synaptic 5HT1A & 5HT4 receptors as well as desensitization of presynaptic inhibitory 5HT1A ones or indirectly through increase release of brain derived neurotropic factors and vascular derived growth factors.

On the contrary, this is in contradiction with others who demonstrated that acute stress is associated with reduced *5-HTT* mRNA levels in raphe nucleus (24). This contradiction may be solved by difference in stage of stress.

This work also revealed deterioration of other markers of depression namely explanatory behavior on open field which measure the ability of animals to recognize stimuli and working memory required for recognition of surrounding environment this is in conformation with former studies (25). Moreover, the locomotor behavior of tested animals in their cages which is directly proportion to state of mood (26) was also decreased. This may be related to inhibition of 5HT₂ receptor as a result of serotonin deficiency (27 & 28) as evidenced by the former work (25) which demonstrated that iontophoretic blockade of 5-HT_{2A} decreases firing for preferred directions and modestly increases firing for non-preferred directions. On the contrary, 70% depletion of serotonin in the principal sulcus does not cause working memory or locomotor impairments on the delayed alternation task (29). This controversy explained by the fact that working memory and locomotor behavior is regulated by other neurotransmitters such as

norepinephrine through α_2 receptors (30), dopamine through D1 receptors (31) and acetylcholine through muscarinic receptors (32).

Treatment of stress induced depressive rats with desvenlafaxine in equivalent doses to human ones resulted in improvement of all parameters of depression namely positive struggle in forced swimming test and rat suspension, decrease in latency period, increase in frequency crossing of central square and total number of crossed squares. The tested drug was more effective in tail suspension test and central line crossing which were normalized. Other parameters were partially improved, they were significantly better compared with non-treated stressful depressive rats but still worse than normal values. This is in accordance with the study done 2014 (19) which showed that desvenlafaxine decreased immobility time in forced swimming test in mice and rats.

The observed antidepressant effect of desvenlafaxine in this work was associated with marked suppression of gene expression of serotonin transporter, so desvenlafaxine blocks serotonin reuptake. This is in agreement with others (33) who showed that desvenlafaxine blocks both serotonin and norepinephrine transporter but contradicted

with the previous work (34) which showed that serotonin transporter knock out and 5HT1A receptor knockout rats had longer period of immobility after forced swimming and more active exploratory behavior on open field test. The work of the late study (34) may represent acute anxiety mediated by mild short term increase in serotonin release as a result of inhibition of presynaptic 5HT1A. The released serotonin could promote anxiety through stimulation of 5HT2C receptors. The antidepressant effect observed in this work may be mediated by profound long term release of serotonin mediated by promotion of neurogenesis of serotonin releasing neurons through the effect of 5HT1A postsynaptic receptor stimulation on releasing brain derived neurotrophic and vascular derived growth factors.

The aforementioned assumption was supported by a research done in 2019 (35) which confirmed that increased brain serotonin may produce initial anxiety reaction mediated by 5HT2c receptor stimulation. (36) Showed that the antidepressant action of most of antidepressant drugs is correlated with down-regulation of 5HT2 receptors which is in line with previously mentioned assumption.

Moreover, desvenlafaxine exerted a late antianxiety mood elevating effect manifested by increase locomotor behavior of animals in cages and exploratory behavior in open field. This may be explained by the previously mentioned observation of (36) who correlated the antidepressant effect of tested drug by compensatory down-regulation of 5HT₂ receptors. The tested drug produced a surprising increase in locomotor activity of tested animals compared to normal ones. This can be explained by the effect of cold water used in forced swimming test. (37) showed that desvenlafaxine increased cold sensitivity which may promote locomotor behavior.

This work revealed that sodium butyrate exerted weaker antidepressant effect than desvenlafaxine. The tested drugs decrease immobility time in forced swimming and tail suspension tests compared with either non treated stressed rats or normal rats. This reflected partial improvement of mood. Open field test showed partial improvement of cognitive exploratory behavior manifested by significant decrease in latency time and increase in line crossing and central line crossing. This is in agreement with studies which demonstrated an antidepressant effect in forced swimming and tail suspension models which were

associated with increase gene expression of brain derived neurotrophic factor and 5HT brain concentration (38). This was associated with significant decrease in gene expression of serotonin transporter which increases serotonin concentration in synaptic cleft (39).

The mechanism by which sodium butyrate inhibited expression of serotonin transporter gene is related to its action as histone deacetylase inhibitor which exerts an epigenic regulatory role on gene expression by two opposite mechanisms. Chromosomes are condensed in compact inactive form by attraction between +ve charge of NH₃ group of lysine in histone and negative charge of phosphate in DNA. Histone acetylation by histone acetyltransferase removes positive charge on histone which relaxes the connection of histone. This may result in either activation or suppression of gene expression. The former is mediated by facilitation of binding of RNA polymerase. The latter is mediated by either facilitation of binding of transcription repressor factors or acetylation of transcription factors (40).

The adopted model of stress had deleterious cardiovascular effects represented by significant rise in congestion, interstitial edema and hemorrhage which may be mediated by stress induced perivascular

inflammation (41) with consequent increase in capillary permeability, interstitial edema (42)

Desvenlafaxine reduced area of hemorrhage in cardiac histopathologic study (43). This may explained by the vasculo-protective effect of serotonin reuptake inhibitor which reversed the vascular damage produced by chronic stress as well as improvement of cardiac contraction through increase norepinephrine release (33).

On the other hand, sodium butyrate exerted marked but weaker cardioprotective effect than desvenlafaxine on tested histopathological parameters probably due to NFkB mediated anti-inflammatory effect (44).

Regarding the cardiovascular effects of sodium butyrate and desvenlafaxine combination on tested model of stress induced depression, it exerted cardioprotective effect which was markedly more potent than sodium butyrate but weaker than desvenlafaxine. This may be attributed by pharmacokinetic antagonism through the inducing effect of sodium butyrate on metabolizing enzyme of desvenlafaxine.

Conclusion:

This work addressed a new aspect for treatment of depression depending on

modifying gene expression of depression related gene. It emphasized the role of desvenlafaxine and sodium butyrate as antidepressant drugs. The drug combination is not recommended because of the presence of pharmacological interaction.

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