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Research Article

Combined Antidepressant Effect of Acetyl-L-Carnitine and Bupropion against Experimental Animal Model

Jagamohan Padhy[1], Pradeep K. Samal[1*], Rajesh Choudhary[2], Jaya Shree[2], Bharti Vaishnaw[1]

[1]*Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India.*
[2]*Department of Pharmacology, Shri Shankaracharya College of Pharmaceutical Sciences, Shri Shankaracharya Professional University, Bhilai, Chhattisgarh, India.*

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ABSTRACT

Depression is one of the most common mental diseases characterized by mood disorders affecting around 322 million individuals in the world. Depression is a feeling of inadequacy, dejection, anhedonia, and decreased activity in any action. Previously acetyl-L-carnitine reported beneficial effects on lipid metabolism, neuroprotection, and some types of depression. Therefore, in the present study, we evaluated the combined effect of acetyl-L-carnitine and bupropion against experimental-induced depression. Albino rats were divided into different groups (each group contained six animals). Normal groups received saline (1 mL/kg, i.p.). The standard group received imipramine (20 mg/kg, i.p.). The ALC group received acetyl-L-carnitine (100 mg/kg, i.p.), and the BPR group received bupropion (20 mg/kg, i.p.). T I and T II groups received acetyl-L-carnitine (30 mg/kg, i.p.) + Bupropion (10 mg/kg, i.p.) and acetyl-L-carnitine (80 mg/kg, i.p.) + Bupropion (30 mg/kg, i.p.), respectively. Antidepressant effects were assessed by forced swim test and sucrose preference test. In both models, the combined effect of the drug produced a significant ($p < 0.05$) antidepressant action as compared to the depression control group. Based on the findings, the combined effect of acetyl-L-carnitine and bupropion had a better therapeutic effect to combat depression as compared to individual treatments.

INTRODUCTION

Depression is a severe mental illness with a mood disorder that is characterized by an unfavorable mood and a lack of interest in activities. It may have an impact on a person's motivation, thoughts, behavior, feelings, and sense of well-being. People who are depressed may feel defeated, and hopeless, and even have suicidal thoughts. It can either be short-term or long-term.[1] The primary symptom of depression is said to be anhedonia, which refers to less curiosity or a loss of feeling of pleasure in any activities.[2] Depression is one of the prominent causes of disability worldwide. More than 300 million people worldwide suffer from depression, according to the United Nations Health Organization; most of these people are women, children, and the elderly. According to research from the UN World Health Organization (WHO), which shows an 18% increase in the number of persons with depression between 2005 and 2015, 4.4% of the world's population suffers from depression.[3] Depression is of many types such as mild, moderate, recurrent, major, seasonal affective disorder, perinatal depression, and psychotic depression. The risk factors that raise the likelihood of depression include the following: A person's level of depression may be affected by life events, personality changes, or their social environment. Some medications may also cause sadness, and family history may also raise the likelihood of depression.[4]

Disruptions to the circadian rhythm or biological clock may be linked to depression. The group of neurotransmitters known as monoamines consists of serotonin, dopamine,

***Corresponding Author:** Dr. Pradeep K. Samal

Address: Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India.

Email ✉**:** samalpharmacology@rediffmail.com

Tel.: +91-7752260027

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norepinephrine, and epinephrine. The monoamine theory of depression posits that an imbalance in particular neurotransmitters is what causes depression and even links specific neurotransmitters to specific depressive symptoms. In people with depression, the monoamine oxidase-A (MAO-A) enzyme that breaks down monoamines may be overactive. Reduced monoamine levels could result from this. The prefrontal cortex is frequently hypoactive in people with depression.[5] In people with major depressive illness, the amygdala, a brain region involved in emotional processing, appears to be overactive.[6] Hippocampal atrophy is observed during depression, which is consistent with research on stress and neurogenesis in animals.[7]

Recently, various reports demonstrated that modulation in lipid metabolism is associated with neuroplasticity, which occurs in depressive patients.[8] It is well documented that carnitine has potential beneficial effects on neuroplasticity.[9] Acetyl-L-carnitine (ALC) is a short-chain ester of carnitine, commonly consumed as a dietary supplement, with the potential to enhance energy levels and muscle strength. It has a variety of effects on the metabolism of the brain and muscles, protecting against neurotoxicity, and may be beneficial in treating some types of depression. ALC is used for carnitine deficiency, treatment of neuropathic pain, etc.[10] Moreover, recent studies showed the potential beneficial effects on depression.[9] It also causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors.[11]

A norepinephrine/dopamine-reuptake inhibitor (NDRI), bupropion lengthens the duration of action and intensifies the effects of these neurotransmitters by weakly inhibiting the enzymes involved in their reuptake. It binds selectively to the dopamine transporter (DAT) and the norepinephrine transporter (NET). Bupropion is categorized as an atypical antidepressant since it has a different effect than traditional antidepressants.[12] In the current research, we examined the combined effects of ALC and bupropion in depressive animal models. Bupropion acts *via* norepinephrine–dopamine reuptake inhibitor with no serotonergic activity. However, its effects on dopamine are weak. Bupropion shows its effect as an antidepressant but the efficacy is low. The common antidepressant-associated side effects, such as sexual dysfunction, weight gain, and sedation, are not associated with bupropion therapy.[13] Therefore, in the current research, we examined the combined effects of ALC and bupropion in depressive animal models keeping in view to increase the efficacy and minimize its side effects.

Material And Methods

Drugs and Chemicals

Acetyl-L-carnitine (ALC) was procured from TCI Chemical (India) Pvt. Ltd., Chennai, India. Bupropion was obtained as a gift sample from Alembic Pharmaceuticals Ltd., Vadodara, India. Imipramine was obtained as a gift sample from *Abbott* Healthcare Pvt. Ltd., Baddi, India.

Experimental Animals

Experiments were carried out on male/female Wistar rats (150–200g, 10–12 weeks of age). The animals were purchased from Chakraborty Enterprises (Reg. no.- 1443/ PO/b/11/ CPCSEA). The animals were habituated in standard laboratory conditions for one week before being tested. They were accommodated under control conditions (25 ± 2°C temperature, with 55 ± 5% humidity and 12 hours light/dark cycle), as per the guidelines of the Committee for Control and Supervision of Experiments on Animals (CCSEA) (Reg. NO.- 994/GO/Re/S/06/CPCSEA). The animals were fed with a standard pellet diet and water ad libitum under hygienic conditions. Before using animals in the trials, the Institutional Animal Ethics Committee (IAEC) of the SLT Institute of Pharmaceutical Sciences, GGV, Bilaspur (C.G), India, gave its approval (Reference No.-179/IAEC/Pharmacy/2016). The experiments on animals were conducted under strict compliance with the ethical principles and guidelines provided by CPCSEA, Government of India.

Wistar rats (150–200 g) of both sexes were acclimatized before the experiment. After the habituation of handling and the laboratory condition, animals were divided into various groups containing six animals (n = 6) in each group. Before experimentation, the body weight of the animals was measured for drug administration calculation. The preparation of all drug solutions involved dissolving them in normal saline and the dose selection was based on earlier studies.[14-16] For evaluation of antidepressant activity, an acute model, i.e., forced swim test (FST), and a chronic model, i.e., Sucrose preference test for measurement of stress-induced anhedonia was chosen. Detailed test procedures are described as follows:

Forced Swim Test

One of the most popular tests for assessing the effects of antidepressants and identifying symptoms of depression is the forced swim test (FST). A mouse or rat is put inside an impenetrable water-filled cylinder during the FST. The animal initially struggles, swims, and climbs, but soon assumes a floating or stationary posture. FST immobility has been regarded as a sign of behavioral hopelessness or entrapment, and practically all antidepressants can be used acutely to alleviate this effect.[17] Each rat was housed in a cylindrical tank, which was filled with 30 cm of 30°C water and measured 40 cm deep and 27 cm in diameter. The water was replaced after each session. The animals were made to swim for 15 minutes (as a pre-test), and then again for 5 minutes the following day. A 5-minute swimming session was preceded by a 1-hour treatment.

The animals of the normal group were treated with saline (1-mL/kg via the i.p route). The standard group was

administered imipramine (20 mg/kg, via the i.p. route). The animals in the ALC group were treated with acetyl-L-carnitine (100 mg/kg, i.p.), and the BPR group was treated with bupropion at 20 mg/kg through i.p. route. T I and T II groups were treated with acetyl-L-carnitine (30 mg/kg, i.p.) + Bupropion (10 mg/kg, i.p) and acetyl-L-carnitine (80 mg/kg, i.p.) + Bupropion (30 mg/kg, i.p.), respectively. Swimming was well-defined as the movement of the forelimbs and hind limbs without the front paws breaking the surface of the water.[18,19] The lack of any movement other than what was required to keep the head and nose above the water is referred to as the immobility phase. The antidepressant-like action of a drug is represented as a reduction in the duration of immobility.[20]

Sucrose Preference Test for Measurement of Stress-induced Anhedonia

Exposing rats to chronic, mild, and unpredictable stressors resulted in a decline in open-field performance and was accompanied by noticeable hormonal changes. This effect could be prevented through the concurrent administration of various antidepressant drugs, whereas drugs from other classes did not have the same effect.[21] Rats have a natural tendency toward sweet solutions. So when they were exposed to both the sucrose solution and normal drinking water they preferred the sucrose solution. Animals subjected to a chronic stress regime were shown to exhibit altered behavior in open fields, as well as a refusal to increase their fluid intake in response to the addition of sugar to their water. This is a particularly important result since it simulates the anhedonia that is a key component of endogenous depression and suggests a malfunctioning reward system.[21]

Procedure

During the experiment, the assessment of fluid consumption occurred in the animals' home cages between 10-11 A.M every Sunday. Before the testing, the animals were deprived of food and water for 23 hours as part of the experiments. Fluid intake was measured using graduated bottles with a scale ranging from 1 to 280 ml. Additionally, 72 hours before each experiment began, the animals were subjected to a continuous 48-hour exposure to two bottles: one containing a 1% sucrose solution and the other with tap water. On either the left or right side of the feeding container, the bottles were counterbalanced. After determining baseline intakes, the groups were separated (n = 6), and their sucrose consumption was matched. Each group underwent a modified stress regimen that was repeated for six consecutive weeks, and a two-bottle fluid preference test was conducted at weekly intervals.[21] The following stressors were used to induce stress: (1) Food and, (2) Water deprivation, (3) Cage tilt (30°), (4) Soiled cage (100 mL water spilled onto bedding), (5) Exposure to an empty water bottle following a period of water deprivation, presence of a foreign object in the home cage, (e.g., piece of wood or plastic). Details of the schedule are given in Table 1.

At the end of the 3rd week of chronic stress, each group received treatment for a further 2 weeks, daily at 9:00 AM. Normal and stress/control groups received saline at 1-mL/kg *via* the i.p. route. The standard group was treated with imipramine at 20 mg/kg *via* the i.p. route. The ALC group received acetyl-L-carnitine at a dose of 100mg/kg via the i.p. route. The BPR group received 20 mg/kg *via* the i.p. route. T I and T II groups were treated with acetyl-L-carnitine (30 mg/kg, i.p) + Bupropion (10 mg/kg, i.p) and acetyl-L-carnitine (50 mg/kg, i.p) + Bupropion (20 mg/kg, i.p), respectively.

Sucrose consumption is analyzed both as total intake and as the amount consumed per gram of body weight. Preference was calculated using the following formula:

Treatment with antidepressants reduces the anhedonia by increasing the percentage preference for the sucrose solution.

Statistical Analysis

The results were expressed as mean ± standard error of the mean (SEM). The significant differences between multiple groups were statistically analyzed by using analysis of variance (ANOVA). The data were considered statistically significant at $p < 0.05$. Statistical analysis was performed using Graph Pad Prism 5.0 software (GraphPad Software, Inc., USA).

RESULTS

Effect on Immobility Period in the Different Experimental Groups of Forced Swim Test

Results obtained from the forced swim test (FST) are represented in Fig. 1. When compared to the normal

Table 1: Schedule of various stressors used to induce chronic mild stress for a period of 5 weeks

S. No.	*Day*	*Time duration (Hours)*	*Stressor name*
1	Mon (10 AM – 5 PM)	7	Cage tilt (30°)
2	Tue (4 PM) – Wed (9 AM)	17	Soiled cage
3	Wed (1 PM) – Thurs (9 AM)	20	Food deprivation
4	Thurs (11 AM – 6 PM)	7	Cage tilt (30°)
5	Fri (4 PM) – Sat (9 AM)	17	Foreign object in the cage
6	Sat (1 PM) – Sun (8 AM)	19	Food & water deprivation
7	Sun (8 AM – 9 AM)	1	Empty water bottle
8	Sun (10 AM – 11 AM)	1	Sucrose preference test

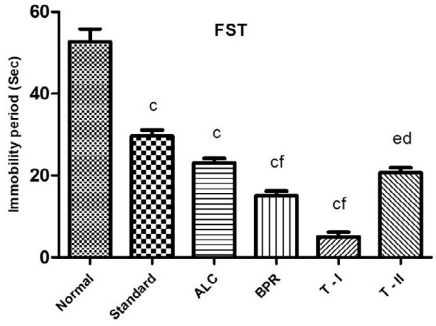

Fig. 1: Effect on immobility period in the different experimental groups of forced swim test. Values are expressed as mean ± SEM (n = 6). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$ when compared to normal group and $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$ when compared to standard group

group, all other groups showed a significant decrease in the immobility period (IP) ($p < 0.001$). When compared with the standard group BPR group and T-I group showed a significant decrease in IP ($p < 0.001$) whereas the T-II group showed a slightly lesser effect ($p < 0.01$). As compared to individual treatment groups with combined groups results suggest that combined groups had better effects. Results show that T-I had the least immobility period, i.e., 5.00 ± 1.15 second. So, we can say that T-I has better anti-depressant effects as compared to other treatments.

Effect on Percentage Preference in the different Experimental Groups of Sucrose Preference Test

The result obtained from the sucrose preference test (SCT) is represented in Table 2. On week 1 there was a moderate decrease in percentage preference (PP) in the control group ($p < 0.01$). As compared to the normal group, on week 2 there was a slight decrease in PP in the standard, and ALC groups ($p < 0.05$) there was a significant decrease in the control, BPR, T-I, and T-II groups ($p < 0.001$). Further significant decreased PP ($p < 0.001$) in all other groups except the normal group on week 3 indicates the inducement of stress. There was a progressive decrease in PP in the control group ($p < 0.001$) from week 1 onwards up to last week. On week 4 slight increase in PP in the standard, ALC, and T-I groups ($p < 0.01$), and a moderate increase in PP in the BPR group ($p < 0.05$).

In week 5 all treatment groups showed a significant increase in PP ($p < 0.001$) as compared to the control group and no significant difference was found in treatment groups as compared to normal groups. As compared to individual treatment groups with combined groups results suggest that combined groups had better effects. Among all treatment groups T-I [(ALC (30 mg/kg) + Bupropion (10 mg/kg)] illustrated better PP (86.32 ± 0.94) in week 5 which indicates better antidepressant properties.

Discussion

With a lifetime risk of 10% in the general population, mood illness is one of the most crippling mental disorders. Many of the medications that are currently being used to treat depression have a negative impact on the patient's quality of life. That causes the patient to refuse the medication, which makes the situation more complicated.[5,22] In this present study, we chose two drug combinations i.e. acetyl-L-carnitine (ALC) and bupropion for the evaluation and assessment of antidepressant activity. ALC, the short-chain ester of carnitine, is synthesized in these organelles endogenously in the mitochondria and peroxisomes and is necessary for the movement of acetyl moieties across their membranes.[23] ALC's actions range from neuroprotective, neuromodulatory, and antioxidant properties to gene expression regulation. ALC is currently being suggested for the management of neuropathic pain due to its variety of effects and great safety and tolerability profile.[24] Bupropion is an atypical antidepressant currently accepted as an aid in smoking cessation and for the treatment of depression and seasonal affective disorder. Bupropion obstructs the reuptake of catecholamine, dopamine, and norepinephrine.[25] Though bupropion is a good

Table 2: Effect on percentage preference in the different experimental groups of SCT

Group	%Preference					
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Normal	84.93 ± 4.65	85.71 ± 2.95	88.34 ± 3.35	87.50 ± 3.65	85.23 ± 2.97	86.55 ± 4.56
Control	77.27 ± 2.85	73.22 ± 1.93^{b}	64.28 ± 3.41^{c}	68.26 ± 1.23^{c}	64.02 ± 0.95^{c}	59.06 ± 3.21^{c}
Standard	86.65 ± 1.98	80.00 ± 2.31	78.26 ± 1.45^{ae}	69.56 ± 0.94^{c}	71.42 ± 2.23^{b}	78.32 ± 1.64^{f}
ALC	82.56 ± 2.57	80.00 ± 1.62	78.26 ± 3.54^{ae}	65.71 ± 4.25^{c}	71.42 ± 0.85^{b}	76.93 ± 2.13^{f}
BPR	84.32 ± 3.21	78.93 ± 1.36	70.66 ± 2.54^{c}	69.60 ± 0.86^{c}	74.32 ± 0.32^{ad}	84.20 ± 1.04^{f}
T - I	81.23 ± 1.53	77.77 ± 2.89	71.68 ± 3.21^{c}	65.00 ± 4.62^{c}	71.79 ± 1.35^{b}	86.32 ± 0.94^{f}
T - II	83.22 ± 2.35	76.23 ± 1.50	69.32 ± 4.61^{c}	66.32 ± 2.23^{c}	70.34 ± 0.59^{c}	75.45 ± 0.93^{af}

Values are expressed as mean ± SEM (n = 6). Data were analyzed by two-way ANOVA followed by Bonferroni's post hoc test. $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$ when compared to normal group and $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$ when compared to control group.

antidepressant but has adverse effects that may limit its use. So, in the present study, we approached combining the bupropion with ALC to enhance the therapeutic efficacy.

The antidepressant medications are frequently tested using the FST and TST models of depression. All major groups of antidepressant medications, such as tricyclics, serotonin selective reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants, are fairly specific and quite sensitive to these tests.[26] In the present study, we used the FST model to assess the effect of drugs by observing immobility time. It is well known that antidepressant drugs reduce the immobile periods,[27] which is reflected in our study. Results showed that the drug-treated group showed a significant reduction in immobility period as compared to the saline-treated group. The results also showed that the T – I group had the least immobility period. So, we can conclude that T – I [ALC (30 mg/kg) + Bupropion (10 mg/kg)] possesses a better anti-depressant effect as compared to individual drugs as well as the standard drug imipramine (20 mg/kg). The possible mode of action might be due to an increase in the level of serotonin, norepinephrine, and dopamine in the animal's nerve terminals causing an increase in swimming behaviors in the FST. Inhibiting the brain's monoamine oxidase (MAO) activity may result in a rise in all three neurotransmitters.[28] A plethora of research suggested that ALC supplementation resulted in improved energy metabolism and sparing of glucose in both hippocampal formation and cortex in mice and increased levels of the norepinephrine and serotonin (5-HT) in the hippocampal formation and cortex were also reported. These two elevated monoamines might be involved in the antidepressant activity of ALC.[29] Moreover, ALC may modulate neuroplasticity which is associated with depression.[8,9] Bupropion functions as a moderate antagonist for nicotinic acetylcholine receptors and inhibits the reuptake of the catecholamine neurotransmitters dopamine and norepinephrine. Bupropion prevents synaptic dopamine and norepinephrine from being reabsorbed when it is acutely supplied peripherally. This action causes brief variations in the brain's extracellular levels of dopamine and norepinephrine, and it may also have an impact on the activity of neurons that release these neurotransmitters.[14] So, we can conclude that the probable antidepressant activity by the T-I group is due to the above-stated mechanism.

The sucrose preference test is also used to evaluate the antidepressant activity. The sucrose preference test for animals is based on the animal's natural preference for sweets, with the assumption that this preference is in proportion to the pleasure that the animal experiences when it consumes them. Most commonly, saccharin or sucrose solutions are used; the advantage of saccharin is that any preference for this solution is presumably based on its taste, and not on its caloric content. When someone exhibits a diminished response to a reward, such as by consuming a tasty sucrose solution, it is typically assumed that the incentive's effectiveness has decreased.[30, 31] This is also thought to represent changed brain function in the reward-mediating brain circuits. It has been reported that such altered responses model the hedonic deficit--anhedonia--which characterizes depressive disorders in humans.[32] In the present study, we used the sucrose preference test for the evaluation of stress-induced anhedonia. It was observed that when animals were exposed to chronic mild stress there was a steady decrease in sucrose preference when compared to their respective baselines. In the third week of the stress protocol, we observed a significant decrease in sucrose preference. The experiments revealed a lower sensitivity to rewards, which may be analogous to anhedonia, the inability to feel pleasure.[33] Therefore, we can conclude that there was induction of depression in all experimental groups except the normal group as per the sucrose preference data. As the treatment started on the 4th week onwards it was observed that there was an increase in declined sucrose preference in all experimental groups except normal and control groups. Reversal of sucrose preference is considered an antidepressant property of drug treatments. So, it was observed that all the treatment groups may possess variable antidepressant properties. From the data obtained from the sucrose preference test, it was found that among all treatment groups, T – I [(ALC (30 mg/kg) + Bupropion (10 mg/kg)] shows better PP (86.32 ± 0.94) in week 5 which indicates better antidepressant property. It was also noticeable that it showed better effect as compared to individual drug as well as standard drug Imipramine (20 mg/kg). So, we can predict that the effect of T – I group may be due to combined administration of ALC and bupropion.

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