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Original Research Article

Ketamine but not glycine potentiates antidepressant like action of citalopram in mice exposed to chronic mild stress

Veena Verma*, Pankaj P. Sonone, Ashish K. Mehta, Chakra D. Tripathi

Department of Pharmacology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

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***Correspondence:**
Dr. Venna Verma,
Email: veenaverma123417@rediffmail.com

ABSTRACT

Background: The present study was designed to investigate the effect of citalopram, ketamine, glycine and their combinations on animal models of depression.
Methods: Swiss Albino male mice were subjected to chronic mild stress for 6 weeks for inducing depression, and randomly divided into different groups: citalopram (5 and 10 mg/kg), ketamine (17.5 and 35 mg/kg), glycine (50 and 100 mg/kg), ketamine (17.5 mg/kg) + citalopram (5 mg/kg) and ketamine (17.5 mg/kg) + glycine (50 mg/kg). Two behavioural tests were utilized for the assessment of depression, namely tail suspension test (TST) and forced swim test (FST). Immobility time was recorded for 6 min, before and after administration of drug.
Results: Citalopram (10 mg/kg) administration caused significant decrease in the immobility time in TST model only but not in FST. Citalopram (5 mg/kg) and ketamine (17.5 mg/kg) caused insignificant decrease in immobility time in both the models. Moreover, ketamine in combination with Citalopram significantly reduced the immobility time in both the models. Glycine at a dose of 100 mg/kg (but not 50 mg/kg) significantly increased the immobility time in both the models as compared to control group. Further, ketamine when administered with glycine caused increase in the immobility time on both the paradigms, though insignificant.
Conclusions: Ketamine demonstrated antidepressant like action in both TST and FST models. Moreover, it potentiated the antidepressant effect of citalopram that might be due to the role of NMDA receptors.

Keywords: NMDA, Ketamine, Citalopram, Glycine, Depression

INTRODUCTION

Depression is a serious health problem in India and worldwide, significantly contributing to morbidity as well as mortality, along with extremely high socioeconomic burden. Patients suffering from depression experience increased percentage of relapse, continuous residual symptoms, functional damage, and an escalation in suicidal tendencies.[1]

The precise etiopathology of depression is still not identified, however the monoamine hypothesis largely explains the cause of depression.[2] Despite the availability of wide range of antidepressants, treatment of depressive illness largely remains unsatisfactory due to various reasons. Firstly, majority of patients showed differential efficacy of at least 20% to multiple antidepressants at adequate doses leading to refractoriness in some patients.[1,3] Secondly, there is generally a period of "therapeutic lag" lasting 3-4 weeks following initiation of antidepressant drug treatment before a measurable therapeutic response becomes evident. This therapeutic delay is critical since it can be associated with increased incidence of suicide.[4] Moreover, antidepressants like

tricyclic antidepressants are associated with severe side effect due to which patient often drop out from treatment.[4] Therefore, efforts to find a novel antidepressant with reliable safety, and fast onset of action, for patients with demonstrating little or no response to the already available standard treatment, still continues unabated.

In this pursuit, the N-methyl-D-aspartate (NMDA) receptors have been considered very crucial in the management of many neurological and psychiatric disorders like major depression and anxiety. Numerous preclinical and clinical studies have suggested that targeting NMDA receptor with selective antagonist like ketamine may enhance the antidepressant response and reduce the therapeutic delay compared to the currently used antidepressants.[5,6] Moreover, several preclinical studies have reported antidepressant like activity with MK-801(non-competitive antagonist) and CGP 37849 (a competitive antagonist) when given either alone or in combination with conventional antidepressants.[5]

However, some amount of uncertainty exists on the assumption that antidepressant effects of Ketamine are largely due to blockade of NMDA receptor (NMDAR). Firstly, some preclinical studies have shown greater and persistent antidepressant activity with R-ketamine than with S-ketamine, even though S-ketamine is believed to be almost 4 times more potent than R-ketamine at causing blockade of NMDA-R, thus challenging the hypothesis of ketamine's antidepressant action via NMDA receptors.[7,8] Also, MK-801, an NMDA receptor antagonist, which binds to the same receptor site as ketamine, did not show antidepressant effects in animals.[7,8] Recent clinical trials also suggested failure of other NMDA-R antagonists to produce ketamine like rapid and sustained antidepressant effects.[6,8,9]

Furthermore, D-cycloserine and rapastinel (GLYX-13), which are partial agonists at the NMDA glycine site, have shown to decrease depressive symptoms without causing psychotomimetic or dissociative side effects.[9,10] Therefore, necessitating further investigation to exactly define the contribution of NMDA-R blockade to ketamine's unique antidepressant action. Thus, the current study was performed to evaluate the effect of ketamine (an NMDA antagonist) in a rodent model of depression and assessing it by using two behavioural paradigms, viz. the forced swim test (FST) and the tail suspension test (TST). Further, an attempt was also made to investigate the role of glycine which is a co-modulator of NMDA receptor in modulating the antidepressant effect (if any) of NMDA antagonist (Ketamine).

METHODS

Animals

The study was conducted in the Department of Pharmacology. Swiss Albino male mice with weights ranging between 22 and 25 g were used for the study. The animals were housed in standard laboratory conditions (12-h light/dark cycle, 21±1°C, and relative humidity of 55±5%), with free access to food and water. Following an acclimatization period of 7 days, the mice were divided as per the different experimental groups that consisted of 6-8 mice per group. All the experiments were performed between 0900 h and 1500 h. The procedures in this study were conducted in accordance with the present CPCSEA Guidelines for the Care and Use of Laboratory Animals.

Drugs

Citalopram and Glycine were procured from Sigma Aldrich, India, while Ketamine and Normal Saline were obtained from the departmental store, VMMC and Safdarjung Hospital. All the drugs were freshly prepared in 0.9% saline before administration.

Chronic mild stress (CMS)

The CMS protocol will be applied to each mouse in an unpredictable manner which includes a variety of low-grade stressors administered over a period 6 weeks.[11] The presentation of different stressors is an essential feature of the model, as repeated presentation of a single stressor results in rapid behavioural habituation. The CMS regime includes soiled cage, tilting of the cage, alterations of the light-dark cycle, periods of food or water deprivation, grouping etc. CMS induces symptoms of major depression that parallel symptoms observed in human depression and different antidepressants reverse these symptoms. The animals will be exposed to each stressor for a short time (few hours to a day) over 6 weeks as shown in (Table 1).

Table 1: Day-wise stressor pattern.

Day	Stress 1	Stress 2
Monday	Noise (85 dB, 3 h)	Cage tilting (45º, 7 h)
Tuesday	Crowded housing (12 animals per cage, 24 h)	Overnight illumination 12 h
Wednesday	Cage tilting (45º, 7 h)	Soiled cage 24 h
Thursday	Dark room 12 h	Food deprivation 24 h
Friday	Noise (85 dB, 3 h)	Soiled cage 24 h
Saturday	Noise (85 dB, 3 h)	water deprivation 24 h
Sunday	Cage tilting (45º, 7 h)	Overnight illumination 12 h

*These stressors will be changed randomly every week

Study design

Animals were divided into the different treatment groups, and the antidepressant effect was assessed by FST and TST. The drugs were administered intraperitoneally (IP) 60 min prior to the test session. The control group received 0.9% saline. Single dose of Citalopram (10 mg/kg), Ketamine (35 mg/kg) and Glycine (100 mg/kg) was administered to each animal. The doses for glycine and ketamine were finalized after performing pilot studies. The citalopram dose was used from previously published literature.[12] In the combination studies, the dose of each drug was reduced to half.

Behavioural tests

Forced Swim Test (FST): The forced swim test is a well-defined screening test for potential antidepressant drugs.[13] This model works on the principle of behavioural despair in which the animal makes futile attempts to escape from the situation, and eventually becomes immobile. The mice were placed in a cylindrical container (30 cm height x 20 cm diameter) with water filled up to 15 cm height, and their mobility and immobility behaviour is recorded. The dimensions of the tank are such that the animals' paw and tail do not touch the tank floor.

Two swimming sessions were performed and recorded using video camera, i.e., a training session of 15 min on the first day followed by a test session of 6 min on the second day, and the period of immobility was recorded.

Tail Suspension Test (TST): In TST, the mice are suspended 50 cm above the floor by adhesive tape just about 1 cm from the tip of the tail.[14,15] After a short period of initial struggling, it becomes completely immobile and motionless. A test session of 6 min was performed, and the period of immobility was recorded.

Statistical analysis

The data are expressed as mean±SEM, and analysed using one-way analysis of variance (ANOVA) followed by Tukey's multiple range test, p values less than 0.05 were considered significant.

RESULTS

Tail suspension test

Mice subjected to CMS were observed to have significant reduction in mobility on TST. Both ketamine (35 mg/kg, IP) and citalopram (10 mg/kg, IP) when administered individually, showed a significant attenuation of the immobility period as compared to the control group (Figure 1). Moreover, the decline in the immobility time was more pronounced with ketamine (135 s) than with the citalopram (165 s). Further, the ketamine (17.5 mg/kg) and citalopram (5 mg/kg) caused non-significant decrease in the immobility time. On the other hand, glycine (50 and 100 mg/kg IP single dose) showed increase in immobility time, and decrease in struggle as compared to control group.

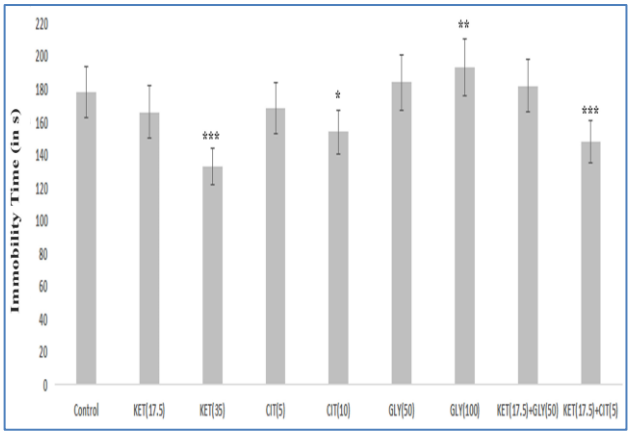

Figure 1: Effect of Ketamine (KET), Citalopram (CIT), Glycine (GLY), KET + GLY, and KET + CIT on immobility time in TST model. Values are expressed as Mean±SEM. Data was analysed by one-way ANOVA followed by Tukey's multiple range test, *p<0.05; **p<0.01; ***p<0.001 as compare to control (Normal saline).

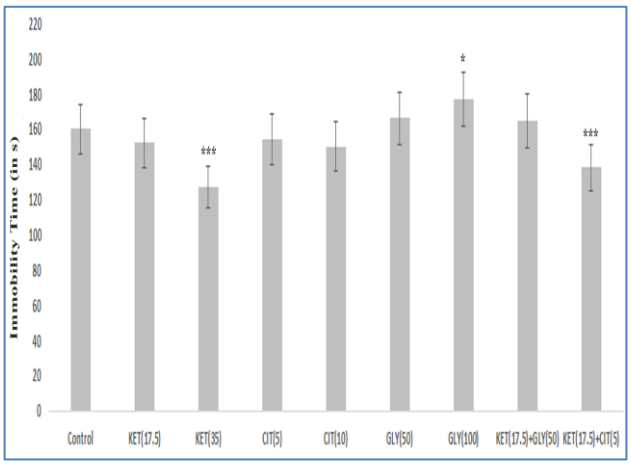

Figure 2: Effect of Ketamine (KET), Citalopram (CIT), Glycine (GLY), KET + GLY, and KET + CIT on immobility time in FST model. Values are expressed as Mean±SEM. Data was analysed by one-way ANOVA followed by Tukey's multiple range test, *p<0.05; **p<0.01; ***p<0.001 as compare to control (Normal saline).

On administration of citalopram (5 mg/kg, IP) along with ketamine (17.5 mg/kg, IP), a significant reduction in immobility period was observed as compared to the control group. This decline in immobility time was more prominent when compared with citalopram (10 mg/kg, IP) alone. However, when glycine (50 mg/kg, IP) was given in combination with ketamine (17.5 mg/kg, IP), an increase in the immobility time was observed when compared with control group, though insignificant.

Forced swim test

The stress-induced mice had decreased mobility that was significant. The administration of ketamine (35 mg/kg, IP) significantly reduced the immobility time as compared with control group, while citalopram alone (5 and 10 mg/kg, IP) and ketamine (17.5 mg/kg) also decreased the immobility time but the effect was not significant (Figure 2). On the other hand, glycine (50 and 100 mg/kg, IP) demonstrated a rise in immobility time as compared with the control group.

Further, the combination of citalopram (5 mg/kg, IP) with ketamine (17.5 mg/kg, IP) demonstrated significant reduction in immobility time as compared to the control group. However, when glycine was administered in a dose of 50 mg/kg, IP with ketamine (17.5 mg/kg, IP), no significant change in immobility time was observed as compared to the control group

DISCUSSION

Depression is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. The currently available therapies for major depressive disorder (MDD) usually take several months to exert their effect, and a large number of patients do not show improvement even after the treatment.[4] Therefore, drugs with improved efficacy and fast onset of action are required. In this context, the N-methyl-D-aspartate (NMDA) receptor antagonists have shown impressive antidepressant effects in clinical trials where ketamine was observed to decrease symptoms in treatment-resistant depressed patients within a few hours, and may sustain for up to 14 days.[6] Initially, our results showed that depression-like behavior was observed in the CMS-induced mouse model, as suggested by a shortened immobility time in TST and FST. Accordingly, a previously reported study has demonstrated that after CMS, numerous impairments in mood, cognition, and memory, and decreases in hippocampal neurogenesis were observed. There was also cortical and limbic brain region atrophy, excessive activation of the noradrenergic system, increases in hippocampal inflammatory proteins, and hypothalamic-pituitary-adrenal axis disturbances.[16] Due to its close resemblance to the behavioral characteristics of patients with depression and related emotional disorders, CMS is considered the most commonly applied and reliable method for a rodent model of depression.[17] In the present study, we have used citalopram (SSRI), ketamine (NMDA receptor antagonist) and glycine to investigate their possible antidepressant action. Apart from this, we also studied the effect of combination of ketamine with citalopram and glycine in animal paradigms of depression. Both FST and TST are validated behavioural tests for the evaluation of probable antidepressant effect of a novel substance.[18]

In the present study, citalopram (10 mg/kg, single dose IP) when tested for its antidepressant effect, demonstrated a significant attenuation in the immobility period in TST, the result of which are similar to a study performed by Sanchez and co-workers where a single dose of paroxetine, fluoxetine, fluvoxamine and citalopram was used.[19] Antidepressant action of SSRI's is majorly due to inhibition of serotonin transporter, thereby causing elevated serotonin levels at the postsynaptic receptor site because of reuptake inhibition.

In our study, Citalopram (10 mg/kg) showed significant activity only in TST but not in FST. Similar finding was also reported in other studies, in which single dose administration of citalopram, did not demonstrate significant effect on immobility time in FST model, however on chronic administration significant reduction in immobility time was observed.[12,20] Similarly, Cryan and co-workers reported decrease in immobility and increase in swimming behaviour in FST after chronic administration of fluoxetine, suggesting low drug dose or single dose which was initially ineffective becomes effective after chronic treatment.[21]

On the other hand, ketamine when given in single dose of 35 mg/kg, IP, a significant reduction in immobility time was observed on both the FST and TST models. Similar decrease in immobility time was observed by Chaturvedi et al, where they showed that MK-801, ketamine and imipramine reduced the duration of immobility in dose dependent manner, but fluvoxamine was ineffective in decreasing the immobility time in FST.[22] This action of ketamine could possibly be due to the antagonism of the NMDA receptors. The other probability of a decrease in immobility time could be due to an increase in BDNF level.[23] According to Reus et al study, rapid antidepressant action of an NMDA antagonist is due to increase in BDNF level in hippocampus of rats, which was detected by ELISA sandwich assay on acute administration of memantine (NMDA receptor antagonist).[23] This view was further substantiated by Autry et al who found that on acute administration of ketamine there was prompt reduction in depression like behaviour in mice (normal mice), but this effect was not observed in BDNF knock-out mice.[24] This effect was probably due to ketamine mediated NMDA receptor blockade, thereby deactivating elongation factor 2 kinase (EF2) leading to reduced EF2 phosphorylation and inhibition of suppression of BDNF translation. Other mechanism as suggested by Matthew S et al, showed that on acute administration, ketamine exerts its antidepressant effect by activating mammalian target of rapamycin (mTOR), leading to an increase in synaptic signalling protein in the pre frontal cortex.[25]

In our study, the combination of citalopram (5 mg/kg) with ketamine (17.5 mg/kg), showed significant decrease in the immobility time in both the FST and the TST models as compared to the control group. This could be attributed to synergistic activity of citalopram with ketamine, as citalopram (5 mg/kg) when given alone did not

demonstrate significant effect on the immobility time in both the models. Similarly, Chaturvedi et al showed that fluvoxamine (SSRIs) alone failed to modify the duration of immobility time *per se* in FST, however when combined with NMDA antagonist like ketamine & MK-801, it potentiated the decrease in immobility time.[22] This observation was also supported by Rogoz and co-workers, who performed a study to examine the synergistic interactions between three antidepressants (fluoxetine, imipramine, venlafaxine), and three non-competitive NMDA antagonists (memantine, amantadine, neramexane). They showed that when fluoxetine was given alone no effect was observed but on combination with NMDA antagonist, it significantly reduced the immobility time.[26] The possible explanation to this is, that ketamine has high affinity for NMDA receptor, it also has less but potentially relevant affinity for μ (mu) opiates and weak antagonistic activity for dopamine transporter.[27] Additionally, NMDAR agent may potentially affect mood due to their secondary effect on monoamine and opiate.[28-30] This effect of ketamine in combination with citalopram in our study may be attributed to its possible interaction with monoaminergic system.

The glycine dose was finalized after performing pilot experiments in our laboratory. On administration of glycine (500 mg/kg), high mortality in animals was observed, whereas when it was administered in doses of 250 mg/kg and 200 mg/kg, it caused marked decrease in locomotor activity when the animals were subjected to open field test. Therefore, the dose of glycine used in the study was 100 mg/kg, at which significant increase in immobility time was observed in FST and TST. Further, glycine (50 mg/kg, IP), when administered in combination with ketamine (17.5 mg/kg, IP), an increase in immobility time was observed, though the effect was not significant as compared to the control group. Earlier studies performed with GLX-13 (partial agonist at glycine-B site of NMDA receptor) and 7- CTKA (NMDA antagonist at glycine B site) showed antidepressant activity in animal models.[31,32] Earlier studies have reported the antidepressant effect of both partial agonist and antagonist at glycine B site of NMDA receptors. This complicated mechanism behind the glycine B site of NMDA receptor requires further evaluation. Although from our study, we could not conclude whether the glycine at 100 mg/kg acts on glycine A or glycine B site. To elucidate the exact role of glycine in depression, further studies using specific agonist and antagonist at glycine A or glycine B sites are needed to be performed.

CONCLUSION

The study shows that ketamine may have an antidepressant effect as demonstrated in both TST and the FST models. Moreover, ketamine in combination with citalopram potentiated the antidepressant effect of citalopram, which may possibly be due to the role of NMDA receptors and their interaction with the monoaminergic system, while glycine at the studied doses and its combination with ketamine, did not show any antidepressant activity. Future investigation may be directed towards using specific agonists and antagonists at different glycine sites to clearly understand the role of glycine in depression or in modulating the antidepressant like effect of ketamine.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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