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Research Article

Role of NMDA Antagonists in Animal Models of Depression

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Abstract

Background: The glutamate system has been studied in depression recently. This is a different from our previous thinking, which had only focused on the levels of serotonin and norepinephrine. The glutamate system may represent a new platform for the management of depression. NMDA and AMPA are receptors for excitatory neurotransmitter, glutamate. Blocking NMDA increases the activity of another receptor, AMPA and this enhanced AMPA activity is cause for rapid antidepressant action. Amantidine and ketamine being non-competitive antagonists of NMDA receptor is evaluated for their antidepressant activity in this study.

Objectives: The objective of the study was to evaluate the antidepressant activity of NMDA antagonists, amantidine and ketamine in Swiss albino mice.

Methodology: Total of 48 (n=48) Swiss albino male mice were used. They were divided into eight groups of six mice in each group. First four groups received, normal saline 10mg/kg (control), imipramine 10mg/kg (standard) and amantidine 30 mg/kg (test drug-1) and ketamine 50mg/kg (test drug-2) per orally and evaluated for antidepressant activity by tail suspension test (TST) after sixty minutes of oral drug administration. Similarly, remaining four groups received the same drugs and evaluated for antidepressant action by forced swim test (FST) after sixty minutes of oral drug administration. Duration of immobility was observed for 6 minutes in tail suspension test and for 4 minutes in forced swim test for each mouse.

Results: Results were analyzed by ANOVA followed by Post hoc Tukey's test. The mean immobility time for TST and FST after the administration of amantidine (30 mg/kg) was found to be 77.33± 15.05 and 95.17± 20.07 seconds respectively. Similarly, for ketamine (50mg/kg), the mean immobility time was 160.00±26.79 and 117.2±21.8 seconds respectively for TST and FST models. The amantidine and ketamine significantly reduced the immobility time in both the models of depression when compared to control ($p < 0.05$).

Conclusion: Non-competitive antagonists, amantidine and ketamine have significant antidepressant activity in acute models of depression.

Keywords: Amantidine, Forced swim test, Imipramine, NMDA antagonists, Tail suspension test

Introduction

Depression is an affective disorder characterized by low mood accompanied by low self-esteem, and loss of interest or pleasure in normally enjoyable activities. Major depressive disorder (MDD) is a disabling condition which adversely affects not only family, work or school life, sleeping, eating habits, but also general health. In the

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United States, around 3.4% of people with major depression commit suicide, and up to 60% of people who committed suicide had depression or another mood disorder.[1]

Depression is a major cause of morbidity worldwide.[2] Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In most countries the number of people who would suffer from depression during their lives falls within an 8-12% range.[3,4] In North America the probability of having a major depressive episode within a year-long period is 3-5% for males and 8-10% for females.[5,6] Population studies have consistently shown major depression to be about twice as common in women as in men, although it is unclear why this is so, and whether factors unaccounted for are contributing to this.[7] The relative increase in occurrence is related to pubertal development rather than chronological age, reaches adult ratios between the ages of 15 and 18, and appears associated with psychosocial more than hormonal factors.[7]

Researchers have discovered associations between clinical depression and the function of three major neurotransmitters, serotonin, norepinephrine, and dopamine. Most of the conventional antidepressants influence the overall balance of these neurotransmitters within brain which regulate emotion, reactions to stress, and the physical drives of sleep, appetite, and sexuality.[8]

Approximately two-thirds of the depressed patients respond to the currently available medications but the magnitude of improvement is still not satisfactory.[5] Moreover, these drugs have unusual side effects. The society is in need for newer, well-tolerated and more efficacious drugs for depression. Hence, newer potent antidepressant with minimal side effects should be investigated.

Recently, glutamate system in depression was studied. This is a departure from previous thinking on reduced serotonin and norepinephrine levels in depression. The glutamate system may represent a new avenue for treatment and research.[8]

NMDA and AMPA are receptors for the glutamate. A new study in mice by Zarate et al. shows that blocking the NMDA receptor is an intermediate step. According to this study, blocking NMDA increases the activity of another receptor, AMPA, and this increase in AMPA activity is crucial for rapid antidepressant actions. Amantidine and ketamine being non-competitive antagonists at NMDA receptor is evaluated for its antidepressant activity in this study.

Materials and Methods

Animals

Ethical clearance was obtained from Institutional Ethics Committee of J. J. M Medical College, Davangere, Karnataka, India, before conducting the present study. Male Swiss albino mice weighing 25-35gm were used for the study. The mice were inbred in the central animal house of the Department of Pharmacology, J.J.M Medical College, Davangere, Karnataka, India under suitable conditions of housing, temperature, ventilation and nutrition. The study was conducted in accordance with standard CPCSEA guidelines.

Drugs and Chemicals

The drugs imipramine, amantidine and ketamine injection were purchased from institutional pharmacy. The test drugs cap. amantidine (100 mg) was dissolved in distilled water and ketamine injection was diluted in normal saline to get desired concentration for the present study.

Experimental Design

Total of 48 (n=48) Swiss albino male mice were used. They were divided into eight groups of six mice in each group. First four groups received, normal saline (control) 10mg/kg, imipramine (standard) 10mg/kg and amantidine 30 mg/kg (test drug-1) and ketamine 50mg/kg (test drug-2) per orally and evaluated for antidepressant activity by tail suspension test (TST) after sixty minutes of oral drug administration. Similarly, remaining four groups received the same drugs and evaluated for antidepressant action by forced swim test (FST) after sixty minutes of oral drug administration. Duration of immobility was observed for 6 minutes in tail suspension test and for 4 minutes in forced swim test for each mouse.

Tail Suspension Test (TST)

The method was similar to that described by Steru L et al.[9] Animals were suspended upside down on a metal rod at a height of 55 cm from the ground with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Initially the animals tried to escape by making vigorous movements but when unable to escape became immobile. The mouse was considered immobile when it did not show any movement of body and hanged passively. The immobility displayed by rodents when subjected to this kind of unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. The total duration of immobility was noted during 6 minute period. Each mouse was used only once.

Forced Swim Test (FST)

The forced swimming model to test for antidepressant activity was developed by Porsolt RD et al.[10] The model used in the present study was similar to the original method described. The animals were forced to swim in a plastic cylinder measuring 30 X 30 cm containing water at room

temperature to a depth of 20 cm. After an initial 2 minute period of vigorous activity, each mouse assumed a typical immobile posture. The mouse was considered immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility was recorded during next 4 minutes of total 6 minute test. The changes in immobility duration were studied after administering drugs in separate group of animals. Each animal was used only once.

Statistical Analysis

Results are presented as Mean ± SEM. One way ANOVA was used for multiple comparisons followed by Tukey's post hoc test for comparison between groups. For all the tests 'P' value of 0.05 or less was considered for statistical significance.

Results

Table 1 and 2 shows immobility periods of amantidine and ketamine in tail suspension test and forced swim test respectively. The mean immobility time for TST and FST after the administration of amantidine (30 mg/kg) was found to be 77.33±15.05 and 95.17±20.07 seconds respectively. Similarly, for ketamine (50mg/kg), the mean immobility time of 160.00±26.79 and 117.2±21.8 seconds recorded respectively for TST and FST models. For the standard drug, imipramine the immobility period was 86±5.877 and 104.2±4.792 seconds noted respectively for TST and FST. The immobility period of 193.3±8.160 and 199.5±6.587 seconds were found for control group in TST and FST respectively. The amantidine and ketamine significantly reduced the immobility time in both the models of depression when compared to control ($p < 0.05$).

Table 1.Effect of Drugs on Immobility Period in Tail Suspension Test

Group no.	Drug treatment	Number of animals	Dose (kg-1)	Immobility time in (sec) (Mean ± SEM)
1.	Control (Normal Saline)	6	10ml	193.3± 8.160
2.	Imipramine	6	10mg	86 ± 5.877**
3.	Amantidine	6	26mg	77.33± 15.05**
4.	Ketamine	6	50mg	160.00±26.79*

n=6, Observations are Mean±SD. ANOVA followed by Tukey's post hoc test; *p>0.05 (NS); **p<0.05 (S)

Table 2.Effect of Drugs on Immobility Period in Forced swim Test

Group no.	Drug treatment	Number of animals	Dose (kg-1)	Immobility Time (in sec) (Mean±SEM)
1.	Control (Normal Saline)	6	10ml	199.5± 6.587
2.	Imipramine	6	10mg	104.2 ± 4.792**
3.	Amantidine	6	30mg	95.17± 20.07**
4.	Ketamine	6	50mg	117.2±21.8**

n=6, Observations are Mean±SD. ANOVA followed by Tukey's post hoc test; **p<0.05

Discussion

For several decades, the monoamine theory of depression has been predominant with regard to the etiology of the illness and also as the rationale behind the bulk of treatments available for treating depression. Currently, the conventional antidepressants have high degrees of selectivity for the 5-hydroxytryptamine (5-HT) transporter, the selective serotonin reuptake inhibitors (SSRIs) and, to a lesser extent, those with a high degree of selectivity for the noradrenaline transporter, the selective noradrenaline reuptake inhibitors (SNRIs). Despite the potency of drugs, they offer less therapeutic improvement on earlier generations of antidepressants. Although generally having a markedly superior side-effect profile, they are similarly not clinically effective in a significant proportion of patients.[11] Furthermore, SSRIs and SNRIs require a period of 2-3 weeks for their full therapeutic effect.[12] This time lag is undesirable for the patient and sometimes can be a serious consideration in those patients who are at high risk of suicidal tendencies.[11] Although the exact mechanism responsible for this delay in therapeutic onset is still under debate, there is a general agreement that this must involve neuroadaptive changes at the cellular and/or receptor level, leading to net alterations in neurotransmission by causing desensitization of presynaptic auto receptors. [12]

Recently, interest has turned to a potential role of the glutamatergic system in depression, particularly with regard to the NMDA receptor.[13] It has been found that a variety of NMDA receptor antagonists demonstrate antidepressant activity comparable to conventional antidepressants in animal models of the illness. These include both competitive and noncompetitive NMDA receptor antagonists.[14,15] Moreover, most of antidepressants have been demonstrated to alter the NMDA receptor in a manner that would be consistent with a resulting decrease in functional activity at this site.[16-19] Unfortunately, in the case of NMDA receptor antagonists, many of these compounds have very limited value in patients, as a result of extremely poor CNS penetration or unacceptable side effects; although recently Berman et al demonstrated a

long-lasting antidepressant effect of ketamine following intravenous infusion of the drug into patients.[20]

Although ketamine is a high-affinity NMDA receptor antagonist, it has less, but potentially relevant, affinity for the μ opiate receptors and weak antagonist activity for the dopamine transporter.[20] Additionally, NMDA receptor agents may potentially affect mood via known secondary effects on monoamine and opiate systems.[21-23] Profound and transient cognitive deficits and euphoria, as evidenced by increases in BPRS(Brief Psychiatric Rating Scales) scores, were also induced by ketamine infusion, as also observed in other subject populations.[24,25]

All available antidepressants commonly take weeks to begin achieving results, but ketamine alleviates depressed mood almost immediately and exhibit residual antidepressant effect when they were retested after two weeks. Although our findings suggest the potential benefit of further exploration of NMDA antagonists as potential antidepressant agents, clinical applicability of this strategy may be limited by the psychotomimetic effects and the potential for abuse of many of these agents. Conversely, NMDA receptor antagonists without psychotomimetic properties in humans (e.g. memantine, eliprodil, and 1-aminocyclopropanecarboxylic acid) merit testing for antidepressant activity.

Amantadine appears to act through several pharmacological mechanisms, none of which has been identified as the one chief mode of action. It is a dopaminergic, noradrenergic and serotonergic substance, blocks monoaminoxidase A (MAO-A) and NMDA receptors, and seems to raise beta-endorphin/beta-lipotropin levels.[21] However, it is still uncertain which of these actions are relevant in therapeutic doses. It is suggested that amantadine might work as an antidepressant not through one, but through several mechanisms thought to be related to antidepressant activity.

Recently, amantadine and memantine, both are weak NMDA receptor antagonists, have shown to have a synergistic effect with conventional antidepressants in animal models of depression.[22,23] It was also observed that fluoxetine, venlafaxine and imipramine all synergized with amantadine or memantine to give improved performance by rats in the forced swim test. Other study has shown increase in the cortical extracellular 5-HT level following the administration of two weak NMDA antagonists with SSRIs, resulting in the potentiation of antidepressant activity.[24]

Although the underlying neurochemical mechanisms by which weak NMDA antagonists are able to potentiate cortical 5-HT levels are unclear, they could involve direct alterations in serotonergic transmission or effects on synthesis of the transmitter.

Alternatively, amantadine has shown clinical role in Parkinson's disease. This drug has shown to potentiate the activity of L-DOPA decarboxylase as well as inhibiting monoamine oxidase B and increases extracellular dopamine levels.[25,26] Fisher and Starr have also reported regional effects of amantidine on the activity 5-hydroxy-tryptophan decarboxylase in the substantia nigra and striatum of rats. Additionally, amantadine has been reported to increase cerebral 5-HT turnover.[27]

There is also a possible role of immunological dysregulation in the pathogenesis of depression. The combination of amantadine and fluoxetine enhanced the production of the negative immunoregulator interleukin-10. The antidepressive efficacy of a combination of fluoxetine and amantadine given in suboptimal doses may be related to the negative immunoendocrine effects of this drugs.[28]

Conclusion

This study shows amantidine and ketamine have significant antidepressant activity. These drugs can be an alternative to conventional antidepressants with novel mechanism of action. Further clinical studies are required on these NMDA antagonists to find out their efficacy and safety profile.

Conflict of Interest: None

References

1. Pillemer K, Suitor JJ, Pardo S, et al. Mothers' differentiation and depressive symptoms among adult children. *Journal of Marriage and Family* 2010; 72(2): 333-45.
2. Sayers J. The world health report 2001 - Mental Health: New Understanding, New Hope. Bull World Health Organ 2001; 79(11): 1085.
3. Andrade L, Caraveo A. Epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys . *Int J Methods Psychiatr Res* 2003; 12(1): 3-21.
4. Kessler RC, Berglund P, Demler O. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289(203): 3095-105.
5. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age of onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 2005; 62(6):617-27.
6. Murphy JM, Laird NM, Monson RR, et al. A 40-year perspective on the prevalence of depression: the Stirling County Study. Archives of General Psychiatry 2000; 57(3): 209-15.
7. Kuehner C. Gender differences in unipolar depression: An update of epidemiological findings and possible explanations. Acta Psychiatrica Scandinavica 2003;

108(3): 163-74.
8. Faster-Acting Antidepressants Closer to Becoming a Reality. NIMH. 25 July, 2007.
9. Steru L, Chermat R, Thierry B, et al. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl) 1985; 85(3):367-70.
10. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther 1977; 229(2): 327-36.
11. Lieberman JA, Greenhouse J, Hamer RM, et al. Comparing the effects of antidepressants: Consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. Neuropsychopharmacology 2005; 30: 445-60.
12. Blier P, De Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994; 15: 230-6.
13. Trullas R, Skolnick P. Functional antagonists of the NMDA receptor complex exhibit antidepressant action. Eur J Pharmacol 1990; 185: 1-10.
14. Maj J, Rogoz Z, Skuza G, et al. The effect of CGP 37849 and CGP 39551, competitive NMDA receptor antagonists in the forced swimming test. *Pol J Pharmacol* 1992; 44: 337-46.
15. Papp P, Moryl E. Antidepressant activity of noncompetitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur J Pharmacol 1994; 263: 1-7.
16. Paul IA, Nowak G, Layer RT, et al. Adaptation of the N-methyl-D-aspartate complex following chronic antidepressant treatments. *J Pharmacol Exp Ther* 1994; 269: 95-102.
17. Boyer PA, Skolnick P, Fossum LH. Chronic administration of imipramine and citalopram alters the expression of NMDA subunit mRNAs in mouse brain. *J Mol Neurosci* 1998; 10: 219-33.
18. Pallotta M., Segieth J, Whitton PS. Chronic but not acute clomipramine alters the effect of NMDA receptor regulation of dopamine release in the rat frontal cortex. Neurosci Lett 1999; 262: 187-90.
19. Pallotta M, Segieth J, Whitton PS. Chronic clomipramine administration reverses NMDA-evoked decreases in dopamine release in the raphe nuclei. Brain Res 1999; 823: 217-20.
20. Berman RM, Cappiello A, Annand A, et al. Antidepressant effects of ketamine in depressed patients. Bio Psychiatry 2000; 47: 351-4.
21. Huber TJ, Dietrich DE, Emrich HM. Possible use of amantadine in depression. Pharmacopsychiatry 1999; 32: 47-55.
22. Rogoz Z, Skuza G, Maj J, et al. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. Neuropharmacology 2002; 42: 1024-30.
23. Rogoz Z, Skuza G, Kusmidern M, et al. Synergistic effect of imipramine and amantadine in the forced swimming test in rats. *Behavioural and Pharmacokinetic Studies Polish J Pharmacol* 2004; 56: 179-85.
24. Owen JCE, Whitton PS. Effects of amantadine and budipine on antidepressant drug-evoked changes in extracellular 5-HT in the frontal cortex of freely moving rats. *British Journal of Pharmacology* 2005; 145: 587-92.
25. Eltze M. Multiple mechanisms of action: the pharmacological profile of budipine. *J Neural Trans Suppl* 1999; 56: 83-105.
26. Fisher A, Starr MS. Opposite effects of glutamate antagonists and antiparkinsonian drugs on the activities of DOPA decarboxylase and 5-HTP decarboxylase in the rat brain. Brain Res 2000; 868: 268-74.
27. Altagracia M, Rojas P, Kravzov J, et al. Amantadine enhances dopamine and serotonin turnover in the MPTP model of Parkinson's disease. Proc West Pharmacol Soc 1993; 36: 289-91.
28. Rogóz Z, Kubera M, Rogóz K, et al. Effect of co-administration of fluoxetine and amantadine on immunoendocrine parameters in rats subjected to a forced swimming test. Pharmacological Reports 2009; 61: 1050-60.

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