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Original Research Article

Study on Role of Antidepressant Drug in Antipsychotic like Effect of Clozapine in Rats

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ABSTRACT

Background: Clozapine is an atypical antipsychotic drug commonly used in treatment of schizophrenia. However, the exact mechanism of its action is still not clear. The present study was planned to examine the role of antidepressant in antipsychotic like effect of clozapine.
Methods: Sprague–Dawley rats weighing 220–250 g were cannulated for intra cerebroventricular (icv) drug administration and injected with artificial cerebrospinal fluid (aCSF) or clozapine (5, 10 µg/rat icv), imipramine (i.c.v.; 1-6 ug/rat) alone or their combination and evaluated for antipsychotic activity in condition avoidance response test. The results were express as % inhibition of condition avoidance response.
Results: I.C.V. administration of clozapine (10 µg/rat icv) and imipramine (i.c.v.; 6 ug/rat)showed dose dependent suppression of condition avoidance response. Imipramine potentiated antipsychotic effect of clozapine at its effective dose in CAR test.
Conclusion: This study demonstrated the participation of antidepressant drug in antipsychotic like effect of clozapine.

Keyword- Antipsychotic, Cerebroventricular, Schizophrenia, Cerebrospinal fluid

INTRODUCTION

PSYCHOSIS

Psychosis refers to an abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". The psychosis are among the most severe psychiatric disorders, in which there is not only marked impairment of behavior, but also a serious inability to think coherently, to comprehend reality, or to gain insight into the presence of these abnormalities. Patients suffering from psychosis have impaired reality testing, i.e. they are unable to distinguish personal subjective experience from the reality of the external world. Psychosis may be caused by the interaction of biological and psychosocial factors depending on the disorder in which it presents. Migration is a social factor that influences people's susceptibility to psychotic disorders (Hutchinson and Haasen, 2004). The stresses involved in migration include family breakup, the need to adjust to living in large urban areas, and social inequalities in the new country. The brain areas the frontal lobe, temporal lobe, limbic system (specially a cingulate gyrus, amygdala and the hippocampus), and the thalamus are thought to be involved.

People experiencing psychosis may report hallucinations or delusional beliefs, and may exhibit personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in

carrying out the daily life activities. A wide variety of central nervous system diseases, from both external poisons and internal physiologic illness, can produce symptoms of psychosis.

PSYCHOTIC SYMPTOMS:

Common symptoms when psychosis is developing:

- Difficulty Concentrating
- Depressed Mood
- Sleeping too much or not Enough
- Anxiety
- Suspiciousness
- Withdrawal from Family and Friends
- Delusions
- Hallucinations
- Disorganized Speech, Such as Switching Topics Erratically
- Depression
- Suicidal Thoughts or Actions

Psychosis (or psychotic symptoms) may also be found in:

Most people with schizophrenia, some people with bipolar disorder (manic-depressive) or severe depression and some personality disorders.

1. **Schizophrenia:** Schizophrenia is a severe and chronic mental illness, associated with high prevalence. Symptoms of schizophrenia typically emerge during alderson or early adulthood. The symptoms of this disease include positive and negative features. Delusion, hallucinations, disorganized speech and thought disorder are positive symptoms; negative symptoms include withdrawal and flattening of emotional responses. The cause of schizophrenia is still unclear. Few animal models have been established for schizophrenia research. Indirect evidence from human and experimental animals suggests that neurochemicals in the brain are involved in the symptoms of schizophrenia.
2. **Dopamine hypothesis:** The dopamine hypothesis of schizophrenia was proposed in 1965. Of many contemporary theories of schizophrenia, the most enduring has been the dopamine hypothesis. The first formulation of the dopamine hypothesis of schizophrenia proposed that hyperactivity of DA transmission was responsible for the positive symptoms observed in this disorder (Carlson and Lindquist, 1963). This hypothesis was based on the correlation between clinical doses of antipsychotic drugs and their potency to block DA D2 receptors (Creese et.al., 1987). Amphetamine, a chemical capable of releasing dopamine in the brain, can produce acute schizophrenic-like behavior symptoms in human, and can also exacerbate schizophrenic symptoms.

In animals dopamine-releasing agents cause a type of stereotypic behavior resembling the repetitive behaviors seen in schizophrenic patients. Dopamine receptor agonists exhibit similar effects in animals. Dopamine antagonists and drugs that block neuronal dopamine storage can control positive symptoms of schizophrenia and amphetamine-induced behavior changes. The antipsychotic efficacy of dopamine antagonists is correlated with their activity in blocking the dopamine D2 receptors (Strange, 2001). Dopaminergic projections are classically divided in nigrostriatal, mesolimbic and mesocortical systems (Lindvallb and Bjorklund, 1983). The hyperdopaminergic activity responsible for positive symptoms has been suggested to be localised in the areas innervated by the mesolimbic DA system, such as ventral striatum (Stavens, 1973). More recently, increase awareness of the importance of enduring negative and cognitive symptoms in this illness and their resistance to D2 receptor antagonism has led to a reformulation of this classical DA hypothesis. Functional brain imaging studies suggested that these symptoms might arise from altered prefrontal cortex

function (Knable and Weinberger, 1997). A wealth of preclinical studies emerged, documenting the importance of prefrontal DA transmission at D1 receptors (the main DA receptor in the neocortex) for optimal prefrontal cortex performance (Goldman-Rakicer et. al.,2000). These observations led to the hypothesis that a deficit in DA transmission at D1 receptors in the prefrontal cortex might be implicated in the cognitive impairments and negative symptoms of schizophrenia (Davis et. al.,1991; Weinberger,1987).

The course of schizophrenia is typically characterized by recurring episodes of symptoms exacerbation, separated by periods of remissions. Since the recognition in 1952 of the antipsychotic properties of chlorpromazine (Delay et.al., 1952). Antipsychotic medications have fundamentally altered the course and prognosis of the illness. They have proven effective at reducing the severity of symptoms and at preventing episodes of illness exacerbation. Nonetheless these medications suffer from important limitations;

1. While D2 receptor blockade is mostly effective at reducing positive symptoms, a substantial number of patients continue to present psychotic feature such as chronic delusions despite appropriate D2 receptor blocked (Pantelis and Lambert, 2003).

2. D2 receptor antagonism is less effective at reducing negative symptoms, and provides only minimal improvement in cognition

3. These medications are associated with numerous side effects, including motor symptoms directly related to D2 receptor blockade in tuberoinfundibular pathways. Extra pyramidal side effects and the hypodopaminergic state associated with these medications might in fact exacerbate negative symptoms and cognitive impairment.

Other neurotransmitters, including serotonine, glutamate, gamma aminobutyric acid and acetylcholine may also be involved in pathogenesis of schizophrenia. It may be due to the careful orchestration between neurotransmitter systems. Serotonin also important in schizophrenia and it may be that the serotonine system interacts with the dopamine system to modify the way in which it operates. The serotonine receptors which are important in the treatment of schizophrenia are 5-HT1, 5-HT2, 5-HT3. The neurochemical hypothesis of schizophrenia is supported by indirect evidence. Although it is oversimplified, it provides fundamental knowledge for understanding the action of antipsychotic drugs. All antipsychotic drugs exhibit antagonistic effects on D2 receptors. Clinical efficacy of antipsychotic agents is achieved when approximately 80% of D2 receptors are occupied. Blocking function of D2 receptor by antipsychotics can be measured by in vitro experiments, i.e., assessment of the ability to inhibit the binding of a radioactive D2 antagonist to brain membrane fragments. The effect of D2 antagonists can also be measured by assessing the inhibition of amphetamine-induced stereotypic behavior in animals. Different types of drugs show different affinities to dopamine receptors. Some are highly selective for D2 receptors; some are relatively non-selective between D1 and D2 (Seeman, 1987).

Psychiatric syndromes

1. Major Depressive Disorder
2. Dysthymia
3. Bipolar Disorder,
4. Borderline Personality Disorder

DEPRESSION

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being. People with a depressed mood may be notably sad, anxious, or empty; they may also feel notably hopeless, helpless, dejected, or worthless. Other symptoms expressed may include senses of guilt, irritability or anger.

Factors of depression

Life events

Adversity in childhood, such as bereavement, neglect, mental abuse, physical abuse, sexual abuse, and unequal parental treatment of siblings can contribute to depression in adulthood.

Personality

High scores on the personality domain neuroticism make the development of depressive symptoms as well as all kinds of depression diagnoses more likely and depression is associated with low extraversion.

Gender identity and sexuality

Studies have shown that those who fall into minorities due to either their gender identity or sexual orientation (such as those that identify as LGBT), are more prone to depression.

Medical treatments

Depression may also be iatrogenic (the result of healthcare), such as drug induced depression. Therapies associated with depression include interferon therapy, beta-blockers, Isotretinoin, contraceptives, cardiac agents, anticonvulsants, antimigraine drugs, antipsychotics, and hormonal agents such as gonadotropin-releasing hormone agonist.

Substance-induced

Several drugs of abuse can cause or exacerbate depression, whether in intoxication, withdrawal, and from chronic use. These include alcohol, sedatives (including prescription benzodiazepines), opioids (including prescription pain killers and illicit drugs such as heroin), stimulants (such as cocaine and amphetamines), hallucinogens, and inhalants.

Non-psychiatric illnesses

Depressed mood can be the result of a number of infectious diseases, nutritional deficiencies, neurological conditions and physiological problems, including hypoandrogenism (in men), Addison's disease, Cushing's syndrome, hypothyroidism, Lyme disease, multiple sclerosis, Parkinson's disease, chronic pain, stroke, diabetes, and cancer.

IMIPRAMINE (ANTIDEPRESSANT DRUG)

Imipramine was discovered in 1951.It was initially developed as an antihistamine and major tranquilizer for use in patients with schizophrenia; its antidepressant effects were discovered serendipitously when moods of patients improved.

Common side effects of imipramine dry mouth, drowsiness, dizziness, low blood pressure, rapid heart rate, urinary retention, and electrocardiogram changes. Overdose can result in death.

Imipramine affects numerous neurotransmitter systems known to be involved in the etiology of depression, anxiety, attention-deficit hyperactivity disorder (ADHD), enuresis and numerous other mental and physical conditions. Imipramine is similar in structure to some muscle relaxants, and has a significant analgesic effect and, thus, is very useful in some pain conditions. *(Mikkelsen, H; et al., 1995).*

Imipramine was significantly more effective in the sample with psychotic depression compared with the nonpsychotic depressed patients.

CLOZAPINE

8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo [b,e][1,4] diazepine

Clozapine is an atypical antipsychotic drug used in the treatment of schizophrenia, and bipolar disorder. Clozapine works well against positive (e.g., delusions, hallucinations) and negative (e.g. emotional and social withdrawal) symptoms of schizophrenia. The atypical profile of clozapine was initially attributed to its anticholinergic properties, which, along with other unknown features, caused selective depolarization of the DA neurons in the substantia nigra, which project to the dorsal striatum, sparing those of the ventral tegmentum, which project to the cortex and mesolimbic systems. The subsequent evidence that clozapine, compared to other neuroleptic drugs clozapine had some

advantages in addition to producing significantly less EPS and tardive dyskinesia, has attracted enormous interest to clozapine and other subsequently developed atypical antipsychotic drugs.

The effects of clozapine are (a) Absence of tardive dyskinesia; (b) Lack of serum prolactin elevations in humans; (c) Ability to eliminate positive symptoms without exacerbating motor symptoms in patients with Parkinson's disease who become psychotic due to exogenous dopaminergic agents such as levodopa (LDOPA); (d) Ability to decrease or totally eliminate psychotic symptoms in approximately 60% of the patients with schizophrenia who fail to respond to typical neuroleptic drug; (e) Ability to improve primary and secondary negative symptoms; and (f) Ability to improve some domains of cognition in patients with schizophrenia, especially secondary memory and semantic memory (verbal fluency). Some of the atypical antipsychotic drugs have also been shown to be more effective than the typical antipsychotic drugs in improving depression, stabilize mood, and decrease suicidality. These collective advantages of clozapine led to the search for the mechanism involved in these effects.

It is classified as an 'atypical' because of its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug like haloperidol. In particular, although clozapine does interfere with the binding of dopamine at D1, D2, D3, and D5 receptors, and has a high affinity for the D4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyamidal side effects. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors.

MATERIALS AND METHOD

Animals Adult male Sprague–Dawley rats weighing 220-250 g were housed in polypropylene cages in a temperature (25±2 0C), relative humidity (50–70%) and maintained on a 12:12h light/dark cycle (lights on 07:00–19:00 h) and had free access to food and water. All experimental procedure were carried outunder strict compliance with Institutional animal ethical committee according to guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi.

Drugs The following drugs were used: 1.Clozapine 2. Imipramine.

I.C.V. cannula implantation Rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and a 24-gauge stainless steel guide cannula (C313G/Spc, plastic UK) was stereotaxically (David Kopf Instruments, CA, USA) implanted bilaterally/ unilaterally into 1mm above the cerebroventricals using stereotaxic co-ordinates (-0.8 mm posterior, ±1.2 mm lateral to midline and -3.5 mm ventral relative to bregma) (Paxinos and Watson, 1998). The guide cannula were then fixed to the skull with dental cement (DPI-RR cold cure, acrylic powder, Dental Product of India, Mumbai) and secured with three stainless steel screws.

Figure: Stereotaxic apparatus and icv cannulation

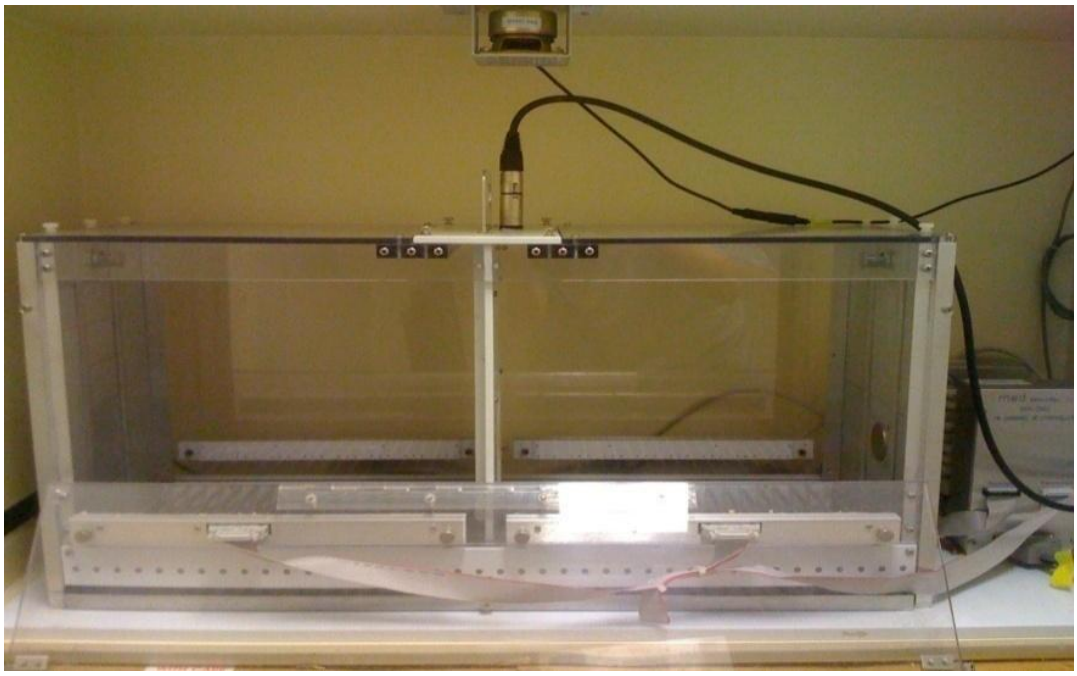
A 22-gauge stainless steel dummy cannula was used to occlude the guide cannula when not in use. Following surgery, the rats were placed individually in cage and allowed to recover at least for 7 days during which the rats were handled to adapt the future experimental conditions. The rats were treated prophylactically with oxytetracyclin (25 mg/kg, i.p.) and neosporin to avoid infection. Animals losing more than 10% of their body weights during recovery period were also discarded (Kokare et al., 2005). Bilateral/unilateral icv injections were given using microliter syringe (Hamilton, Reno, NV, USA) connected by PE-10 polyethylene tubing to a 28-gauge internal cannula (C313I/Spc, plastic one, internal diameter 0.18 mm, outer diameter 0.20 mm) that extended 1 mm beyond the guide cannula. The internal cannula was held in a position for another 1min after each injection to promote diffusion of drugs before being slowly withdrawn to prevent backflow.

Experimental protocols-:

After a recovery period from surgery, animals were acclimatized to the testing environment for 7 days as described in our previous reports (Kotagale et al., 2010; Taksande et al., 2011). Rats were divided in different treatment groups (n=5-6) and injected with vehicle or drugs bilaterally into icv alone or in combinations. Fifteen min following aCSF (0.5 µl), imipramine (1 µg-6µg/rat), clozapine (5, 10 µg/rat), the individual rat was subjected to condition avoidance response. 10 min following last injection and each rat was subjected to condition avoidance response.

Apparatus for CAR:

The shuttle box was constructed of a transparent acrylic sheet and plywood. The box measured 66 cm in length, 33 cm wide and 39 cm in height. The box was divided into two equal compartments by barrier which hadan opening of 10 × 10 × 10 cm. The floor was made up of stainless steel rods placed 0.5 cm apart. There was separate arrangement for condition stimuli (sound and light) and



Condition avoidance response test apparatus

Procedure for CAR:-Rats were train individually to move from one compartment of shuttle box into other upon presentation of the 10-s buzzer tone (condition stimulus;

CS). If the rat failed to respond, the tone was further continue with an unconditioned stimulus (UCS) in the form of an electric shock (0.5 mA) delivered to grid floor of the chamber for a period of 20-s intertrial interval. The trial terminated once the rat moved into the other compartment during C.S. or U.C.S. Crossing made during the condition stimulus period were recorded as avoidance response and those made during UCS period were recorded as escape responses. All animals were trained for a week. Only those animals characterized by a high level of avoidance responding (80%) were used for further experiments. Number of avoidance responses during 10 trials were recorded and expressed as % inhibition of condition avoidance response.

TREATMENT

1. Dose specific effect of imipramine in condition avoidance response:

In these set of experiments the dose dependent effect of imipramine on CAR was investigated. Different groups (n=6) of rats were injected either with Imipramine (i.c.v.; 1-6 ug/rat) or aCSF (0.5 µl/rat icv), 10 min thereafter each rat was subjected to CAR apparatus and number of avoidance response/10 trials was recorded.

2. Dose specific effect of clozapine in condition avoidance response:

In this experiment the dose dependent effect of clozapine on CAR was investigated. Different groups (n=6) of rats were injected either with clozapine (5, 10 µg/rat icv) or aCSF (0.5 µl/rat icv), 10 min thereafter were subjected to CAR apparatus and number of avoidance response/10 trials was recorded.

3. Effect of enhanced endogenous imipramine levels on antipsychotic like effect of clozapine.

Separate group of rats was administered with effective dose combination of clozapine (5µg/rat icv) and imipramine(i.c.v.; 1-6 ug/rat)oraCSF (0.5 µl/rat icv). 10 min thereafter animals were subjected to CAR testing and number of avoidance response/10 trials was recorded.

Statistical analysis-:

The data were expressed as mean ± S.E.M. The results of % inhibition of condition avoidance response were analyzed by one-way ANOVA followed by Dunnett's test. Effects of combinations were analyzed by a one-way ANOVA followed by Newman-Keuls comparison test. Results of statistical tests with $P<0.05$ were considered significant.

RESULT

1. Dose specific effect of clozapine on condition avoidance response

The results presented in Figure 5.1 showed that clozapine given by icv route caused significant suppression of CAR behavior in rats [$F(2,9)=14.18$; $P<0.001$] as indicated by an effect of drug treatment. Post hoc Dunnett's multiple comparison test revealed that clozapine at a dose of 10 µg/rat icv produced approximately 52.5% inhibition of avoidance responding ($P<0.001$), and administration of low dose of clozapine (5 µg/rat icv) did not change CAR response as compared with control group.

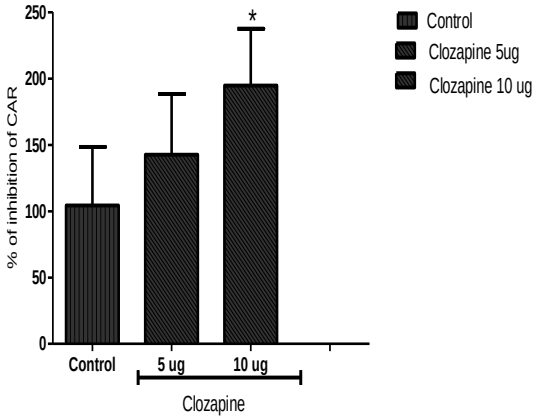


Figure: Effect of clozapine on conditioned avoidance response in rats. Rats were placed individually in the shuttle box for determination of avoidance responses ten min after clozapine injections (5 and 10 µg/rat, icv) or aCSF (0.5 µl/rat, icv), and placed individually in the shuttle box for the

standard ten-trial session. Each bar represents the percentage inhibition of conditioned avoidance response ±SEM for a group (n=6). *P<0.001 vsaCSF treated control rats (one way ANOVA post hoc Dunnett's multiple comparison test).

2. **Dose specific effect of imipramineon condition avoidance response**

The results presented in Figure5.2, showed that imipramine given by icv route caused significant suppression of CAR behavior in rats [F (3,12)=15.45; P<0.0001] as indicated by an effect of drug treatment. Post hoc Dunnett's multiple comparison test revealed that imipramine at a dose of 1µg/rat icv produced approximately 42.5% inhibition of avoidance responding (*P<0.001), whereas at 3µg/rat icv abolished CAR by 65% (*P<0.0001). Administration of low dose of imipramine (6µg/rat icv) did not change CAR response as compared with control group.

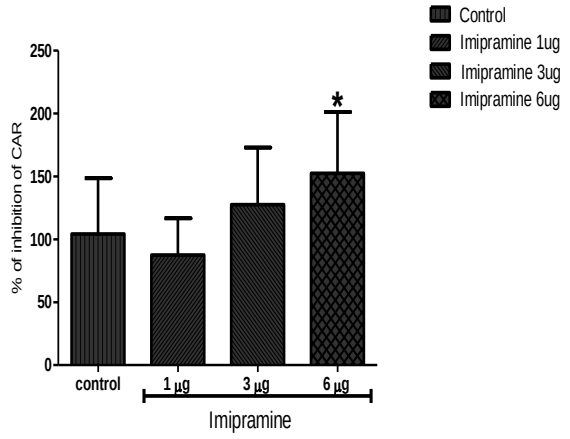


Figure: Effect of imipramine on conditioned avoidance response in rats. Rats were placed individually in the shuttle box for determination of avoidance responses ten min after imipramine injections (i.c.v.; 1-6 ug/rat)or aCSF (0.5 µl/rat, icv), and placed individually in the shuttle box for the standard ten-trial session. Each bar represents the percentage inhibition of conditioned avoidance response ±SEM for a group (n=6). *P<0.001, *P<0.01 vsaCSF treated control rats (one way ANOVA post hoc Dunnett's multiple comparison test).

3. **Effect of clozapine and imipramine combination on condition avoidance response**

The result presented in Figure5.3, showed that combined effect of clozapine and imipramine given by icv route caused significant suppression of CAR behavior in rats [F (3,12)=16.36; P<0.0001] as indicated by an effect of drug treatment. Post hoc Newman-Keuls multiple comparisons test revealed that combination of clozapine (10µg/rat icv) and imipramine (i.c.v.; 6 ug/rat) produced approximately 62.5% inhibition of avoidance responding (P<0.0001) as compared to control group.

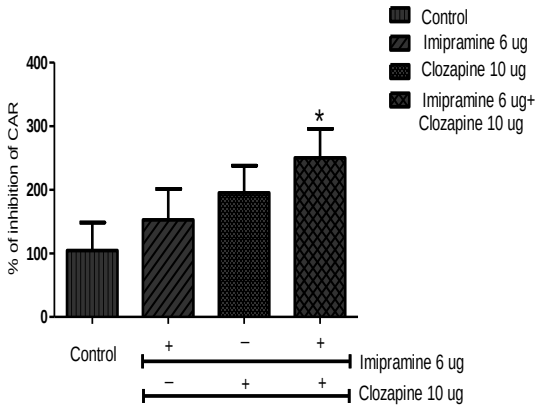


Figure: Effect of combination of doses of clozapine (10µg/rat icv) and imipramine (i.c.v.; 6 ug/rat)or aCSF (0.5 µl/rat, icv) on conditioned avoidance response in rats.Ten min there after rats were placed individually in the shuttle box for the standard ten-trial session. Each bar represents the percentage inhibition of conditioned avoidance response ±SEM for a group (n=6), *P<0.0001vs aCSF, @P<0.001 vs clozapine treated group and #P<0.001 vs imipramine treated group

DISCUSSION

Clozapine is most widely used in treatment of schizophrenia. Despite of lower affinity to dopamine D2 receptor clozapine showed superior efficacy, to ameliorate negative and cognitive symptoms, over

typical antipsychotic. Clozapine also displays significant affinities for several other neurotransmitter receptors, including dopaminergic (D1, D3 or D4), serotonergic (especially 5-HT2A and 5-HT2C), adrenergic (mainly α1) and histaminergic (especially H1) receptors. However its precise mechanism is still poorly understood. In present study we attempted to find the involvement of imipramine in antipsychotic like effect of clozapine. Imipramine showed effect on anxiety and depression *(Mikkelsen, H; et al., 1995).*The result of present study showed that imipramine significantly potentiated the antipsychotic effect of clozapine in CAR.

Condition avoidance response (CAR) is commonly used animal model for prediction of antipsychotic effect. (Wadenberg et al., 2010) that is based on suppression of the avoidance response. In rats CAR shows particular sensitivity, with high predictive validity, for detection of antipsychotic activity of drug. It also shows high affinity as antagonists for brain dopamine receptors, is also sensitive for the detection of potential antipsychotic compounds acting primarily via neurotransmitter receptors other than the DA D2 receptor.

Thus it is possible that clozapine might increase endogenous imipramine level to exhibit antipsychotic like effect.

In conclusion, present study demonstrated the role of imipramine in antipsychotic like effect of clozapine. The result of these findings project action of clozapine mediated through imipramine a new therapeutic alternative to treat psychiatric disorders.

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