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RESEARCH ARTICLE

EVALUATION OF ANTIDEPRESSANT ACTION OF NICOTINE IN AN ANIMAL MODEL

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ABSTRACT

Introduction: Nicotine may have antidepressant properties and smokers self-medicate underlying depression. Epidemiological findings suggest that smokers more often demonstrate depressive symptoms than non-smokers and depressed patients are less likely to cease smoking. **Aim & Objectives:** To evaluate the effect of nicotine given as acute and chronic combination therapy with imipramine in learned helplessness model in rats.

Material and Methods: Learned helplessness model is a standard model for evaluation of antidepressant drugs. The statistical significance was determined by ANOVA followed by Tukey test ($p<0.05$).

Results: In this model, results were expressed as percentage of animals showing presence of escape response. Combination therapy of imipramine (i.p.) with nicotine (s.c.) given for 7 days produced significant antidepressant action as compared to combination therapy of imipramine (i.p.) given for 7 days with single dose of nicotine (s.c.).

Conclusion: It was observed that combination dose of imipramine with nicotine given for 7 consecutive days significantly exhibited antidepressant action by increasing percentage of escape response.

INTRODUCTION

Major Depressive Disorder (MDD) is characterized by feeling of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, lack of pleasure, lowering of self-esteem and agitation. According to WHO, 26% of the population will suffer from depression by the year 2020. Recent available antidepressants used to treat major depressive disorder (MDD) often take weeks to months to achieve their therapeutic benefits, commonly resulting in considerable mental illness and increased risk for suicidal behaviour.[1,2]

There are interesting reports in the literature indicating relationship of smoking/nicotine and depression. Smokers use nicotine to treat depression. Also depressive symptoms are more common in smokers as compared to nonsmokers. It has also been observed that the chances of stopping smoking are less in depressed patients.[3]

Preclinical and clinical data regarding this issue are ambiguous. This study was undertaken to evaluate the antidepressant action of nicotine using the learned helplessness model in rats.

Aim & Objectives

To evaluate the effect of nicotine given as acute and chronic combination therapy with imipramine in learned helplessness model in rats.

MATERIAL AND METHODS

The experimental procedures and protocol for the study were reviewed and approved by the Institutional Animal Ethics Committee (IAEC). The pharmacological experiments were performed as per norms laid by Committee for Control and Supervision of Experimentation on Animals (CPCSEA). Wistar rats ≅ 200-250gm (male/female) housed in polypropylene cages (single rat/cage) were used. (n = 10 in each group). The rats used for this were procured from the animal house located in Dr. D. Y. Patil Medical College, Pimpri, Pune-18, Maharashtra, India.

Antidepressant action of study drugs was evaluated using learned helplessness model in rats.

Study groups:

Group 1: Vehicle only s.c. 1 ml/kg
Group 2: Imipramine 10mg/kg i.p.(7 days)
Group 3: Single dose nicotine 0.4 mg/kg s.c.

Group 4: Acute Therapy - Imipramine 10mg/kg i.p. (7 days) + Nicotine 0.4 mg/kg (s.c.) (Single dose) combination

Group 5: Chronic Therapy- Imipramine 10mg/kg i.p. (7 days) + Nicotine 0.4 mg/kg (s.c.) (7 days) combination

Learned helplessness test[4,5,6]

Cook's Pole Climbing apparatus was used for this model. In this model a helpless situation was created for the rats, which results in performance deficits in subsequent learning task. Repeated shocks (15sec duration 0.8m A every min) for 1 hour were applied and this serves as a stress to the animals. There was no escape route available. It acts as a first phase of model. The 2nd phase was 'conditioned avoidance training'. During this phase the rat was trained for 10 days to avoid the noxious stimuli i.e shock and to climb pole. During this period, study treatment was administered. A buzzer precedes the shock and simultaneously placed pole in the Cook's chamber and rat was allowed to escape towards it and avoid the noxious stimulus (electric shock). This is term as escape response. Failure to exhibit escape response by animal is said to be an indicative of its depressive state. Animals in the following groups were evaluated for reduction in escape failure with study drugs.

In combination treatment, single dose nicotine was administered at the end of seven day administration of imipramine in groups 2 and 3. Seven day administration of nicotine was administered simultaneously along with imipramine in group 4 and group 5. Reduction in escape failure response of rat of study treatment was compared with imipramine treated rats.

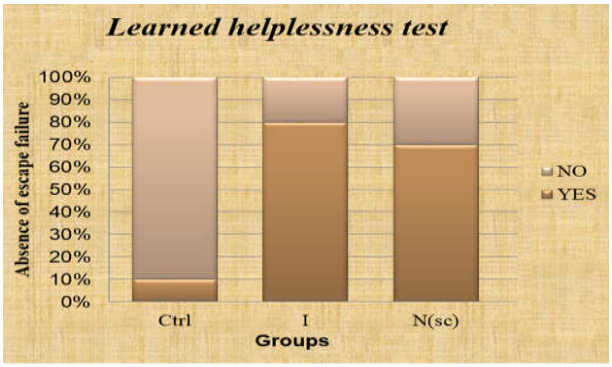
Statistical analysis

The results were expressed as percentage of animals showing absence of escape failure response. The statistical significance was determined by Fishers exact test using Primer of Biostatistics &$p < 0.05$ was considered statistically significant.[7]

RESULTS

Reduction in escape failure response was recorded. Rats were exposed to chronic stress i.e. electric shock. Failure to show escape response from electric shock by animal is said to be an indicative of its depressive state.

In this model of depression, results were expressed as percentage of animals showing absence *of escape failure*. The percentage of animals showing absence *of escape failure* was significantly less in vehicle treated group i.e only 10 percent of rats have shown *absence of escape failure*. In group receiving imipramine and nicotine administered by subcutaneous route, the percentage of animals showing *absence of escape failure* significantly increased as compared to vehicle treated group. Percentage was 80 and 70 with imipramine by subcutaneous route and nicotine by inhalational route respectively.

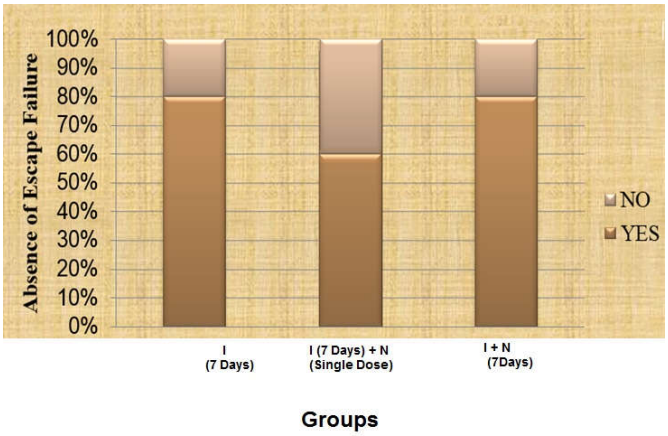


Effects of combination of imipramine(7days) + single dose nicotine on escape failure

Combination of imipramine(7days) with single dose of nicotine

Single dose of nicotine was given in combination with imipramine by s.c. or inhalational route.

Difference between percentage of *absence of escape failure* in these three groups i.e imipramine alone, imipramine + single dose nicotine (s.c.) and imipramine + single dose nicotine(inhal.) was not significant.



Effect of nicotine (7days) with imipramine on escape failure

Nicotine was administered for 7days in combination with imipramine. Nicotine was administered by s.c. route. In group receiving nicotine with imipramine, difference between imipramine alone and combination of nicotine by subcutaneous route with imipramine was not significant.

DISCUSSION

Depression is an important contributor to the global burden of the mental diseases affecting people in all the communities across the world. Today depression is estimated to affect 350 million people.

Major depression is treated with drugs that inhibit the reuptake and metabolism of biogenic amines such as noradrenaline, serotonin and dopamine. Drugs like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) do not exhibit either a faster onset of action or greater efficacy than their predecessors.[8] Therefore, there are concerted efforts underway to develop antidepressants with possible advantages over currently used antidepressant drugs.[9] Depressed smokers are more dependent on smoking and smoking cessation in these subjects is often followed by a depressive episode.[10] Nicotine patches can improve the mood of depressed patients.[11-13]

Available reports regarding antidepressant action of nicotine are controversial. Smoking is the most common route by which nicotine is inhaled and the results of subcutaneous nicotine have been inconsistent in various studies on depression. Laura A Leon suggested that for the sake of precision in animal modeling, animal models like active avoidance, social isolation, learned helplessness, behavioral despair, genetic depression models would be important to evaluate the antidepressant activity of a new potential compound.[14]

Learned helplessness model is a standard model for evaluation of antidepressant drugs. In this model, results were expressed as percentage of animals showing presence of escape response. The most convincing results demonstrating antidepressant like effect of nicotine were reported by Semba *et al* (1998), who showed that the chronic treatment with nicotine produced antidepressant like effect in the learned helplessness model of depression.[15]

However, Ferguson *et al* (2000) reported that nicotine did not influence the learned helplessness response, though a subtype selective nicotine acetylcholine receptor agonist produced antidepressant like effect.[16]

Therefore, we conducted this study that compared the effects of imipramine, a tricyclic antidepressant and nicotine. Nicotine was administered subcutaneously. Before estimation of neurotransmitters in rat brain tissue, rats were isolated for 15 days which induced depression. In this group, serotonin levels were significantly decreased compared to normal rats. Increased levels of 5-HT (serotonin) were seen in groups treated with standard antidepressant drug imipramine and nicotine administered by subcutaneous route.

CONCLUSION

It was observed that combination dose of imipramine with nicotine given for 7 consecutive days significantly exhibited antidepressant action by increasing percentage of escape response.

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