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Pharmacological Studies on Anti diabetic Effect of Papaverine Psychosis Associated Diabetes Mellitus in Sprague-Dawley Rats

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A B S T R A C T
Papaverine is an opium alkaloid of the benzyl isoquinoline group, of low toxicity and non-habit forming. Presently its widest clinical use is in the treatment of conditions associated with smooth muscle spasm. Recent discovery of the high expression of PDE-10A in pancreatic islets may provide a basis for the anti diabetic activity. In this study, male Sprague dawley rats are taken and divided in to four groups viz., control, negative control, and two different doses of test drug (10mg/kg, i.p and 20mg/kg, i.p). High fat high sucrose diet for a period of 6 weeks and weekly once administration of apomorphine(1mg/kg, s.c) is used to induce diabetes and psychosis. Papaverine treatment is started on 21st day after confirmation of elevated blood glucose levels which indicates state of diabetes. The treatment period is continued till the end of the study. The behavioural parameters are evaluated by open field, locomotor activity, stereotypic behaviour and body temperature, weekly once prior to animal sacrifice. Treatment with papaverine at two different doses significantly exhibited antipsychotic and antidiabetic effects on HFHSD and Apomorphine induced rats.

Keywords: Papaverine, Apomorphine, Diabetes mellitus, Insulin Resistance, Oxidative stress, Phosphodiesterase (PDE) inhibitor

A R T I C L E I N F O

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CONTENTS

1. Introduction

Diabetes Mellitus:

Diabetes Mellitus is a chronic metabolic stress disorder characterized by deficiency in insulin secretion or action or both, resulting in hyperglycemia (the elevated circulating glucose levels). The disorder was the first recorded in 1552 B.C., when an Egypt physician diagnosed a patient with polyuria (frequent urination, among the major signs of diabetes mellitus). However, it was in the last century that diabetes mellitus was recognized to exist in two major forms, namely, T1DM (insulin dependent) and T2DM (non-

insulin dependent).The diabetes mellitus is an endocrinal disorder which is growing with jet speed globally. The epidemiological studies indicate that every 3rd person in India is suffering from insulin dependent diabetes mellitus. The multifactorial or multi facet is causing a global problem and waiting for a cure from new chemical entities (NCE) either from medicinal plants or synthesis.

Fig 1: Diabetes mellitus and central nervous system complications

So far, the research core on diabetes mellitus including T1DM has focused on peripheral endocrinology and nervous system. However, the impact of diabetes on the CNS been largely recognized. Among these cognitive and mood related complications have largely been studied in the past investigations.Mental illness is a highly prevalent phenomenon in our society that inflicts an enormous burden of distress on the affected individuals and their families. Among mental disorders, schizophrenia stands out as one of the most severe and disabling conditions affecting roughly 1% of the population worldwide. Regarding the more proximal mechanisms of schizophrenia, contemporary pathophysiological models, assume that psychosis is triggered by dysregulation of dopaminergic activity in the brain. Schizophrenic patients have been reported to eat a diet higher in fat than the general population. High level of fat intake is considered to be an important factor in the development of insulin resistance and obesity. Insulin resistance, often characterized by impaired insulin signal transduction, diminished glucose uptake and dysregulated energy metabolism, is frequently preceded by glucose intolerance and can lead to the development of type2 diabetes. Psychotic illness and its treatment are associated with an increased rate of diabetes and worsening of blood sugar. Metabolic dysfunctions have been associated with antipsychotic treatment including increased levels of circulating leptin and these changes can be an important link between insulin resistance syndromes in subjects receiving antipsychotic drugs. The newer, second generation antipsychotic agents are more likely to produce this effect than the first generation agents, but both contribute to the problem. Among the patients suffering from schizophrenia or other psychotic disorders, the prevalence of diabetes mellitus was 15% and the prevalence of a disturbed glucose tolerance was 14%.

In the present study the pharmacological investigation is designed to evaluate the effect of Papaverine in ameliorating Psychosis associated Diabetes mellitus induced by the combination of high fat-high sucrose diet and apomorphine for about 6 weeks in Sprague-dawley rats were studied.

Papaverine is a nonxanthine phosphodiesterase inhibitor for the relief of cerebral and peripheral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias. The main actions of Papaverine are exerted on cardiac and smooth muscle. Papaverine acts directly on the heart muscle to depress conduction andprolong the refractory period. Papaverine relaxes various smooth muscles. This relaxation may be prominent if spasm exists. The muscle cell is not paralyzed by Papaverine and still responds to drugs and other stimuli causing contraction. The antispasmodic effect is a direct one, and unrelated to muscle innervation. Papaverine is practically devoid of effects on the central nervous system. Papaverine relaxes the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral, and pulmonary arteries.

2. Material and Methods

Drugs and Chemicals: Papaverine, Apomorphine, Glucose, Cholesterol, HDL and Triglycerides kits were purchased from Sigma Chemical Company Inc., St Louis, MO, USA. Glucose oxidase, Phosphate buffer, Magnesium chloride, Heparin, EDTA, Cholesterol esterase, Cholesterol oxidase, Tris-HCl buffer pH- 8.2, Pyrogallol, DETPA, 0.01 N HCl, Ammonium molybdate.

Experimental Animals:

Sprague dawley rats (male) weighing about 150-200 g, divided into 4 groups (n=6) were used for the pharmacological studies. The animals were kept under standard conditions maintained at 23-25^0 c, 40 to 60% humidity, 12hr light /dark cycle and given standard pellet diet, provimi limited (India), provided ad libitum. The animals were acclimatized to the laboratory conditions for a week prior to the experimentation. Principles of animal handling were strictly adhered to and the handling of animals was made under the supervision of animal ethics committee of the institute. The experimental protocol was approved by the animal ethics committee (IAEC).

Experimental Design:

For this study, the animals were divided randomly in four groups with 6 rats per group as following:
Group-I: Control group (vehicle treated)
Group-II:HFHSD and Apomorphine (1mg/kg, s.c.)
Group-III: HFHSD - Apomorphine and Papaverine (10mg/kg, i.p.)
Group- IV:HFHSD - Apomorphine and Papaverine (20mg/kg, i.p.)

Experimental Procedure:

Male Sprague dawley rats were divided into 4 groups, each consisting of 6 animals. Group – I was treated with standard chow diet, group – II, III, and IV were treated with high fat -high sucrose diet. Groups –III and IV were treated with two doses of Papaverine for about 21 days after confirmation of glucose intolerance on 21st day. In order to analyze the antipsychotic effect of drug, behavioral studies like Locomotor activity, Stereotypic behavior, Body temperature, Open field were performed.

Induction of Psychosis and Diabetes Mellitus:

Animals were fed with HFHSD for about 6 weeks, and apomorphine (1mg/kg) was administered subcutaneously, weekly once. Catatonia in Rodents Species: Male Wistar or Male Sprague-Dawley rats, Nonhuman primates (Cebus monkeys).

Freely movable Indicative Behavior: Unusual / Catatonic posture End Point: Neuroleptics induce catatonia / unusual posture Drugs: Haloperidol (1 mg/kg i.p.), Metoclopramide (20 mg/kg i.p.) Brief Procedure Catatonia in rats is defined as failure to correct an unusual (externally imposed) posture for a prolonged period of time. Neuroleptics, which have an inhibitory action on the nigrostriatal dopamine system, induce catatonia. While neuroleptics with little or no nigrostriatal blockade produce relatively little or no catatonic behavior. Animals are dosed intraperitoneally with the testdrug or the standard. They are placed individually into translucent plastic boxes with a wooden dowel mounted horizontally 10 cm from the floor and 4 cm from one end of the box. The floor of the box is covered with approximately 2 cm of bedding material. The animals are allowed to adapt to the box for 2 minutes. After that each animal is grasped gently around the shoulders and under the forepaws. Then it is placed carefully on the dowel. The amount of time spent with at least one forepaw on the bar is determined. This time is recorded as the duration of catatonia. When the animal removes its paws, the time is recorded and the rat is repositioned on the bar. Three trials are conducted for each animal at 30, 60, 120 and 360 minutes. An animal is considered to be catatonic, if it remains on the bar for 60 s or more. Neuroleptics such as haloperidol and metoclopramide induce catatonia / unusual posture. For dose-response curves, the test is repeated with various doses and more animals.

Pharmacological Studies

Behavioral Studies:

Open field test: In order to control for possible effects on locomotor activity, animals were explored to a 40 cm×50 cm×60 cm open field whose brown linoleum floor was divided into 12 equal squares by white lines. In both sessions, the animals were placed in the rear left square and left to explore it freely for 5 min during which time the number of line crossings are counted.

Locomotor activity:

Animals were transferred from their housing facility to the locomotor activity testing room for a habituation period of 15 min before testing. Animals were placed in automated locomotor activity frames i.e., Actophotometer, that created a grid of infrared light beams throughout the equipment. The number of breaks of light beams caused by the moving animal was equivalent to its locomotor activity. Data were collected over a total period of 10 min.

Body temperature:

Rectal body temperature was measured in a temperature controlled room (24 ± 1 °C and 50 ± 10% relative humidity) by inserting a lubricated thermometer into the rectum. Animals were adapted to the experimental situation by measuring body temperature on multiple occasions before studies with vehicle or drug.

Stereotypic behavior:

Stereotypic behavior induced by apomorphine was observed for a period of 10 min immediately after its administration in rats placed in individual plexi glass cages. For scoring streotypies, two scales adapted from Costall and Naylor (1973) were used.

3. Results and Discussion

Effect of Papaverine on the Open-field test:

The results were shown in the Table:1 ; Fig no: 2. the exploratory behavior i.e., the number of line crossings decreased significantly (P<0.01) in negative control group (II) in comparison with the normal diet group (I). The number of line crossings increased significantly (P< 0.01 and P<0.001) in both 10 mg/kg and 20 mg/kg Papaverine treated groups (III & IV) respectively and indicates the open field habitutation.

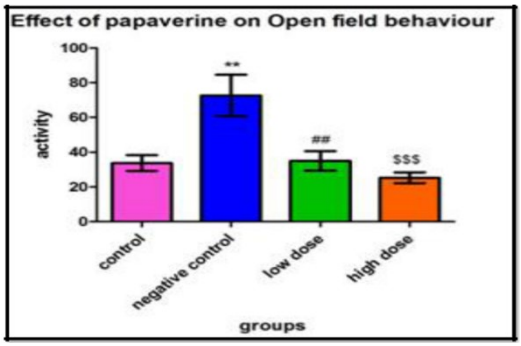

Fig 2: Effect of Papaverine of behavioural measures in the open field test for the drug treatment groups in Sprague dawley rats in comparison with Apomorphine and Papaverine

Effect of Papaverine on the Locomotor activity:

The results were shown in the Table:2 ; Fig no: 3. the locomotor activity estimated using actophotometer has been increased significantly (P< 0.001) in negative control group (II) in comparison with the normal diet group (I). The locomotor activity has been decreased significantly (P< 0.001 and P<0.001) in both 10 mg/kg and 20 mg/kg Papaverine treated groups (III & IV) respectively.

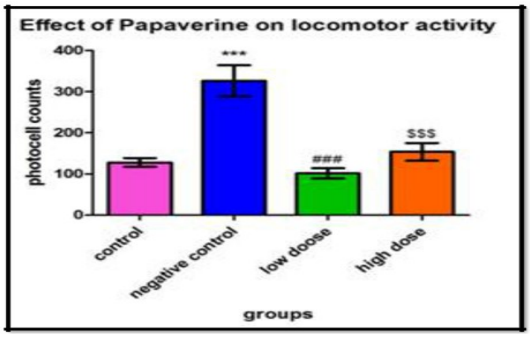

Fig 3: Effect of Papaverine on locomotor activity for the drug treatment groups in Sprague dawley rats in comparison with Apomorphine and Papaverine

Effect of Papaverine on Body temperature:

The results were shown in the Table: 3; Fig no: 4. the body temperature has been decreased (P<0.01) in negative

control group (II) in comparison with the normal diet group (I). The body temperature has increased significantly (P<0.05 and P<0.05) in both 10 mg/kg and 20 mg/kg Papaverine treated groups (III & IV) respectively.

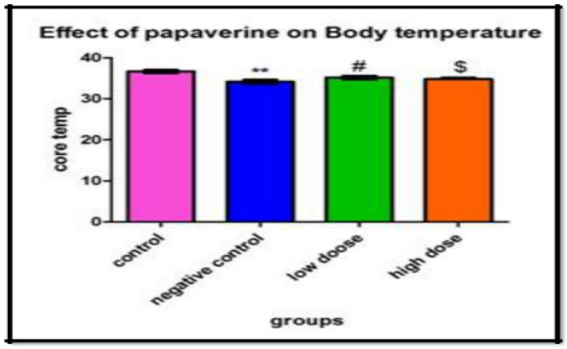

Fig 4: Effect of Papaverine on body temperature for the drug treatment groups in Sprague dawley rats in comparison with Apomorphine and Papaverine. Values are presented as means S.E.M. (n=6)

Effect of Papaverine on the stereotypic behavior:

The results were shown in the Table: 4; Fig no: 5. the stereotypic behaviour has been observed (P< 0.001) in negative control group (II) in comparison with the normal diet group (I). The stereotypic behavior has been reduced significantly (P< 0.01 and P<0.01) in both 10 mg/kg and 20 mg/kg Papaverine treated groups (III & IV) respectively.

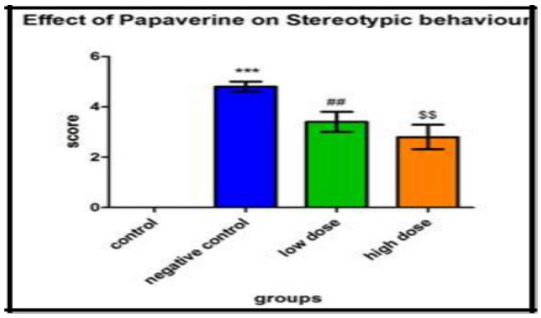

Fig 5: Effect of Papaverine on Stereotype behavior for the drug treatment groups in Sprague dawley rats in comparison with Apomorphine and Papaverine.

Discussion:

The present investigation reveals behavioural abnormalities when the animal is fed with HFHS for 6 weeks. The experimental conditions that yield low base line activity suitable for assessing increase in locomotion produced by apomorphine. Hypermotility involves the stimulation of postsynaptic dopamine receptors localized in limbic structures. On the basis of the hypothesis that extrapyramidal side effects of neuroleptics are linked to the blockade of nigrostriatal dopaminergic transmission, whereas dopamine receptor blockade in limbic structures may be responsible for antipsychotic activity. In our study, treatment with papaverine significantly antagonized the apomorphine induced hypermotility. Apomorphine induced increased line crossings in open field habituation test were antagonized by the two doses of papaverine treatment. But there was less significant improvement in open field habituation with low dose of papaverine when compared to that of high dose treatment. Stereotypies are mediated by activation of postsynaptic dopamine receptors in the striatum.

Treatment with papaverine has significantly antagonized the apomorphine induced stereotypic behavior.The D3 dopamine receptor subtype may play a major part in the apomorphine induced hypothermia. Supporting evidence for this view is also derived from the correlation observed between the potency of neuroleptics to antagonize apomorphine induced hypothermia and their affinity for the D3 receptor. Like conventional neuroleptics, which show higher affinity for the D 2, than for the D3receptor, the papaverine also displayed very less significant antagonistic activity against apomorphine induced hypothermia.

4. Conclusion

In conclusion, we suggest that markedly Papaverine improves Psychosis associated Diabetes mellitus induced by combination of high fat-high sucrose diet and Apomorphine. It was understood from the behavioral studies that Papaverine possesses the activity in reducing the insulin resistance, dopaminergic antagonistic activity and antioxidant effect. From the conclusion, it's revealed that the drug Papaverine could be a therapeutic agent for treating Psychosis associated Diabetes mellitus.

Table 1 Effect of Papaverine on the Open-field behavioural test in SD rats

Groups	Exploratory behavior
Group I (Normal diet)	33.83 ± 4.50083
Group II (HFHSD + Apo)	** 72.67 ± 11.99
Group III (HFHSD + Apo + Papaverine10mg/kg)	## 35 ± 5.62
Group IV (HFHSD + Apo + Papaverine20mg/kg)	$$$25.33 ± 3.08

**p<0.01 indicates comparision of negative control group with control group
##p<0.01 indicates comparision of low dose group with negative control group
$$$p<0.001 indicates comparision of high dose with negative control group.

Table 2 Effect of Papaverine on Locomotor activity in SD rats

Groups	Photo cell counts
Group I (Normal diet)	127.8 ± 10.733

Group II (HFHSD + Apo)	*** 326.5 ± 37.52
Group III (HFHSD + Apo + Papaverine10mg/kg)	### 101.7± 12.36
Group IV (HFHSD + Apo + Papaverine20mg/kg)	$$$ 153.8± 21.41

Table 3 Effect of Papaverine on Body temperature in SD rats

Groups	**^{0}C**
Group I (Normal diet)	37.5 ± 0.5^{0}C
Group II (HFHSD + Apo)	**34.5 ± 0.5 ^{0}C
Group III (HFHSD + Apo + Papaverine10mg/kg)	##35.5 ± 0.5 ^{0}C
Group IV (HFHSD + Apo + Papaverine20mg/kg)	$$ 36.5± 0.5 ^{0}C

Table 4 Effect of Papaverine on the stereotypic behavior in SD rats

Groups	**Stereotypic behavior**
Group I (Normal diet)	0
Group II (HFHSD + Apo)	**4.80± 0.2
Group III (HFHSD + Apo + Papaverine10mg/kg)	##3.40± 0.4
Group IV (HFHSD + Apo + Papaverine20mg/kg)	$$ 2.8 ± 0.48

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