

# ANTIDEPRESSANT ACTIVITY OF DPP-4 INHIBITORS IN ALBINO MICE, AN EXPERIMENTAL STUDY

## Pharmacology

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### Abstract:

**Objective:** To evaluate the antidepressant activity of DPP-4 INHIBITOR in mice.

**Methods:** Sixty adult Swiss albino mice weighing 25-30 grams were selected. Thirty were allocated to forced swim test and thirty to tail suspension test models. In each model there were 6 groups. The control group received vehicle (10 ml/kg, p.o) as standard, Imipramine (10mg/kg p.o) and the other groups received sitagliptin linagliptin, saxagliptin, vildagliptin respectively 1 hour prior to the acute study. In chronic study, the drugs were given orally once a day for 10 days and the last dose was given 1 hour before the experiment. Duration of immobility was noted in forced swim test and tail suspension test. Statistical analysis was performed using Mean +/- SEM. ANOVA followed by Dunnett's test. P< 0.05 was considered statically significant

**Results:** DPP-4 inhibitors produced significant antidepressant effect at all the doses, as indicated by reduction in the duration of immobility compared to the standard. The antidepressant effect was higher with sitagliptin and linagliptin when compared to saxagliptin, vildagliptin and control.

**Conclusion:** DPP-4 inhibitors sitagliptin and lingaliptin has shown significant antidepressant activity greater than imipramine in mice.

**Keywords:** Forced swim test, Tail suspension test, DPP-4 INHIBITORS, Depression, geriatric patients.

### Introduction

Depression is a chronic illness that affects people of all ages. Major depression is a psychiatric disorder in which mood, thought content, and behavioral patterns are impaired, often for an extended period of time. The condition is encountered especially among elderly persons admitted to the hospital and those residing in nursing homes. Although there are many effective antidepressants available today, the current armamentarium of therapy is often inadequate, with unsatisfactory results in

about one-third of all subjects treated. This provides impetus in the search of newer and more effective antidepressants.<sup>1</sup> DPP-4 inhibitors are effective and commonly prescribed drugs for diabetes patients. They have received considerable attention in recent times due to their beneficial effects on multiple physiological systems. After realization of pleiotropic effects of DPP-4, they are being prescribed to patients suffering from cardiovascular disorders like hypertension and ischemic heart disease, irrespective of the lipid profile. DPP-4 inhibitors is the most commonly prescribed

in the world for chronic diabetic resistant patients for insulin.<sup>2,3</sup> Glucose reduction using DPP-4 inhibitors improves memory in some cases but not others. Controversy exists over use of DPP-4 inhibitors to alleviate memory problems in Alzheimer's disease (AD).<sup>4</sup> Correlations of glucose and cognitive function are mixed and association studies find that some genetic polymorphisms are related to cognitive function but others are not.<sup>5</sup> Recently, some concerns are raised regarding effects of DPP-4 inhibitors on memory and psychomotor functions. Hyperglycemia is thus suggested to partly mediate age-related brain changes. Possible link between hyperglycemia and depression has been suggested in both clinical and preclinical studies. The recently proposed entity of vascular depression provides indirect support for hyperglycemia as a risk factor in the path physiology of depression. Since diabetes is more prevalent in geriatric patients, use DPP-4 inhibitors may have beneficial effects on depression. Hence this study was undertaken to find out its role in animal models of depression.

## Materials And Methods

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Chettinad Hospitals and Research Institute, Chettinad University, Chennai, India. Adult male Swiss albino mice weighing 25-35 gm from our breeding stock were used in this study. The animals were housed at  $24 \pm 2^\circ$  C with 12:12 h light and dark cycle. They had free access to food and water. The animals were acclimatized for a period of 7 days before the study. The animals were used according to the CPCSEA guidelines for the use and care of experimental animals. The standard antidepressant drug imipramine, DPP-4 inhibitors drugs like sitagliptin, lingalipitin, saxagliptin and vildagliptin was obtained from our institutional pharmacy. On the day of the experiment, the animals were divided randomly into control and experimental groups (n=6). Group 1 received the vehicle, normal saline (10ml/kg) and served as the control group, group 2 received the standard drug imipramine (10mg/kg), groups 3, 4, 5, 6 received the test drugs DPP-4 inhibitors sitagliptin 10mg/kg oral, linagliptin 5mg/kg oral, saxagliptin 0.5mg/kg oral, vildagliptin 5mg/kg oral respectively. Drugs/vehicle was administered to the animals 60 minutes prior to the evaluation in acute study and for chronic study, a new set of animals were used. They were grouped as in acute study and were administered the drug/vehicle orally once

daily for a period of 10 days. Behavioral evaluation was carried out 60 minutes post drug/vehicle administration on the 10th day.<sup>6</sup> The antidepressant activity of the test drug was evaluated using the experimental models of depression TST and FST

**Tail suspension test (TST):** The method described by Steru, et. al. was used in our study.<sup>7</sup> The animals were hung by the tail on a plastic string 75 cm above the surface with the help of an adhesive tape. The duration of immobility was observed for a period of 8 minutes, last 6 minutes of the observation were taken for calculation. Mice were considered immobile only when they hung passively and were completely motionless.

**Forced Swim Test (FST):** The method described by Porsolt, et. al. was used in our study.<sup>8</sup> Each animal was placed individually in a 5 litre glass beakers, filled with water up to a height of 15 cm and were observed for duration of 6 minutes, last 4 minutes of the observation were taken for calculation. The mouse was considered immobile when it floated motionless or made only those moments necessary to keep its head above the water surface. The water was changed after each test.

**Statistical Analysis:** The mean  $\pm$  SEM values were calculated for each group. The data were analyzed using one way ANOVA followed by Dunnet's multiple comparison test.  $P < 0.05$  was considered to be statistically significant.

## Results

**Tail suspension test (TST):** Results are given in table-1. A significant ( $p < 0.01$ ) decrease in the duration of immobility was seen with the standard drug imipramine and test drug (DPP-4 inhibitors sitagliptin and lingalipitin) in all the tested doses as compared to the control (group 1) in acute study but in chronic study the dose of 5mg/kg of sitagliptin and lingalipitin produced a greater decrease in the duration of immobility as compared to the standard drug imipramine.

**Forced swim test (FST):** Results are given in table-2. A significant decrease in the duration of immobility was seen with the standard drug imipramine and all tested doses of DPP-4 inhibitors as compared to the control (group 1). In acute study, test drug (DPP-4 inhibitors sitagliptin and linagliptin) in a dose of 5mg/kg is more efficacious than imipramine in reducing the duration of immobility.

However in chronic study, DPP-4 inhibitors sitagliptin and linagliptin both the doses tested (5mg and 10mg/kg) was more efficacious than imipramine.

## Discussion

The present studies establish DPP-4 inhibitors (SITAGLIPTIN AND LINAGLIPTIN) have antidepressant activity in laboratory animals like rats as evidence by force swim test and tail suspension method. Alteration in glucose of brain cell membranes may influence membrane fluidity, consequently affecting various catecholamine neurotransmitter systems, including 5-HT (serotonin) and noradrenaline.<sup>9</sup> Preclinical studies have demonstrated that low glucose levels may lead to decreased 5-HT (serotonin) function in the brain through reduced numbers and/or function of postsynaptic 5-HT receptors.<sup>10</sup> In contrast, mechanisms by which glucose depletion may favourably affect the 5-HT system have also been proposed. These include an inverse correlation between platelet 5-HT (serotonin) concentrations and serum glucose levels in patients with hyperglycemia or renal disease; an association between glucose lowering treatment and normalization of initially low intraplatelet 5-HT; and a directly adverse impact of elevated glucose levels on 5-HT transporter or receptor function.<sup>11,12</sup>

The prevalence of unrecognized depression in the geriatric patients was high, especially in those who reported their health as poor.<sup>13</sup> World Health Organization (WHO) in the year 2000 have identified major depressive disorder ranks as the fourth leading cause of death in the world. WHO also estimates that in 2020, the disorder will increase to second only to ischemic heart disease. Dental and oral management conducted in accordance with procedures and have to be carried out carefully especially to patients with mental disorders such as depression. Dental caries, gingivitis, xerostomia, oral candidiasis, and TMJ disorder are clinical findings in depressed patient. Appropriate dental management necessitates a vigorous preventive dental education programme, the use of artificial salivary products, antiseptic mouthwash, daily fluoride mouthrinse and special precautions when administering local anaesthetics with vasoconstrictors and prescribing analgesics.<sup>14</sup> So dentists have to cooperate with psychiatrists in providing comprehensive treatment to improve quality of life of the psychiatric patients.<sup>15</sup>

## Conclusion

The results of the present study have shown that DPP-4 inhibitors SITAGLIPTIN AND LINAGLIPTIN have antidepressant activity better than imipramine. SITAGLIPTIN AND LINGALIPTIN has the potential to be used as an adjuvant in the treatment of depression. Further pre clinical and clinical studies may help to elucidate the possible mechanisms of action of SITAGLIPTIN and lingliptin.

**Table 1:**  
**Effect of DPP-4 inhibitors on immobility time in the Forced Swim Test (FST) using mice**

Group (Drug Treatment)	Duration of Immobility (in seconds)	
	Acute Study	Chronic Study
Group 1 (Normal saline 10ml/kg)	120.83 ± 7.19	128.17 ± 15.02
Group 2 (Imipramine 10mg/kg)	88.16 ± 9.02	82.16 ± 12.15
Group 3 (Sitagliptin 10mg/kg)	53.16 ± 6.40***	49.50 ± 6.80 ***
Group 4 (Lingliptin 5mg/kg)	62.83 ± 12.51***	64.33 ± 7.84
Group 5 (Saxagliptin 0.5mg/kg)	50.15 ± 2.20	45.50 ± 3.0
Group 6 (vildagliptin 5mg/kg)	70.00 ± 6.66**	68.66 ± 12.73

Values represented mean ± S.E.M. (n=6), \*\*P<0.001 vs. STD (group 2).

**Table 2:**  
**Effect of DPP-4 inhibitors on immobility time in the Tail Suspension Test (TST) using mice**

Group (Drug Treatment)	Duration of Immobility in (sec)	
	Acute study	Chronic study
Group 1 (Normal saline 10ml / kg)	230.33 ± 9.11	209.5 ± 13.54
Group 2 (Imipramine 10mg/kg)	167.00 ± 7.21	153.5 ± 12.35
Group 3 (sitagliptin 10mg/kg)	124.17 ± 12.46***	124.17 ± 12.46***
Group 4 (lingliptin 5mg/kg)	147.17 ± 14.68**	138.17 ± 29.96**
Group 5 (saxagliptin 0.5mg/kg)	120 ± 15.66	130 ± 5.80
Group 6 (vildagliptin 5mg/kg)	151.33 ± 5.98	143.67 ± 8.57

Values represented mean ± S.E.M. (n=6), \*\*P<0.001 vs. STD (group 2).

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