Research Paper

Effect of Gliclazide on Motor and Cognitive Function in Haloperidol Induced Parkinson's Disease with Diabetes Mellitus as Co-Morbidity in Wistar Rats

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Type 2 diabetes mellitus, an endocrine disorder, and Parkinson's disease, a neurological condition, are common diseases that negatively affect individuals' quality of life. The incidence of Parkinson's disease is typically higher in diabetic individuals than in non-diabetic individuals. Several studies have reported that the use of hypoglycemic agents (such as glibenclamide, tolbutamide, and glipizide) is associated with a reduced risk of Parkinson's disease in diabetic individuals. This study evaluated the effect of gliclazide in an experimental rat model. Rats were given a high-fructose diet for 14 d, followed by intraperitoneal administration of alloxan to induce diabetes, mimicking human conditions. All diabetic rats then received intraperitoneal haloperidol for the next 7 d to induce Parkinson's disease. The drug-treated group additionally received gliclazide. The effects of gliclazide on motor and cognitive functions were evaluated using the rotarod test, bar test, inclined plane test, Y-maze, and Morris water maze. Study findings showed that gliclazide counteracted the effects of the haloperidol and fructose-fed alloxan regimen on motor and cognitive function, as evidenced by a significant reduction in cataleptic score, latency time to reach the top of the inclined plane, and improved fall-off time in the rotarod test. Additionally, gliclazide reduced the latency to find the hidden platform in the Morris water maze and increased the percentage of alteration behavior in the Y-maze. In light of these results, gliclazide, a sulfonylurea, appears protective and could be a candidate for clinical trials in individuals using antidiabetic drugs, particularly those with early-stage Parkinson's disease.

Key words: Diabetes mellitus, gliclazide, haloperidol, alloxan, neurological condition, Parkinson's disease

Parkinson's Disease (PD) is the world's second most common neurodegenerative disease after Alzheimer's disease[1,2]. With a globally aging population and increasing life expectancy, the prevalence of PD is projected to more than double between 2015 and 2040[3]. PD is a chronic, progressive neurodegenerative disorder characterized by movement impairments (motor akinetic-rigid syndrome) and non-motor symptoms such as depression, constipation, and sleep disturbances. Untreated, PD progressively worsens over the years, leading to rigidity, breathing difficulties, and an increased risk of infections[1-5]. Research suggests that a complex interplay of genetic and environmental factors, including exposure to heavy metals and pesticides, contributes to PD risk. The disease results from the degeneration of dopamine-producing neurons in the Substantia Nigra (SN), leading to dopamine deficiency in the brain. The prevalence of PD increases with age, affecting approximately 1 % of individuals over 65 and 4 %-5 % of those over 85[5-8]. The disease prevalence ranges from 41 cases per 100 000 in individuals in their 40s to more than 1900 cases per 100 000 in those aged 80 and above. According to the study by Komici *et al.*[9], the prevalence of Diabetes Mellitus (DM) in PD individuals was 10.02 %. Furthermore, DM individuals exhibited a higher risk of developing PD compared to non-DM individuals, and PD individuals

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with DM demonstrated greater severity of motor symptoms[9]. The prevalence of Type 2 DM (T2DM) among PD individuals varies slightly, ranging from 3.4 % to 9.1 %[10], while the prevalence of PD in the general population is 1-2 per 1000 individuals[11].

The association between DM and PD was firstly reported in 1993 by Sandyk. He proposed that diabetes may intensify the severity of the motor symptoms and reduce the therapeutic efficacy of drugs used to treat PD[12]. Several studies have also demonstrated that T2DM and PD both are major risk factors for development of PD and T2DM respectively, which has been confirmed in different ethnic groups[13-19]. There are many similarities between both conditions T2DM and PD[20]. The important relationship between insulin and dopamine emerges even more in the brain reward system, involving mesolimbic dopamine pathway[21]. Dopamine plays a central role in food reward, energizing feeding and reinforcing food seeking behavior[22-23] and substantial body of evidence showed that insulin modulates the reward circulatory[24]. Additionally, numerous studies have shown shared mechanisms underlying DM, insulin resistance, and PD[11]. Some studies have revealed that impaired insulin signaling in dopaminergic pathways and exacerbated neurodegeneration in animal models could facilitate the onset of PD-like symptoms[25-27]. Furthermore, long-term hyperglycemia in a rat model has been shown to cause nigrostriatal dopaminergic neurodegeneration due to elevated oxidative stress, resulting in motor impairments similar to early parkinsonian symptoms[28].

Additionally, numerous studies have demonstrated the beneficial effects of antidiabetic agents in PD[20]. Insulin, the primary therapy for DM, plays a crucial role in PD progression through various pathways. By binding to its receptor, insulin is essential for neuronal protection during development[20]. Researchers have also reviewed the potential role of antidiabetic agents in PD treatment. Furthermore, oral hypoglycemic drugs, such as biguanides, sulfonylureas, and thiazolidinediones, have been found to be beneficial in managing individuals with PD[29-32]. Sulfonylureas (such as glibenclamide, tolbutamide, and glipizide) act as secretagogues, stimulating insulin release by inhibiting ATP-sensitive K^+ (K^+ATP) channels in pancreatic Beta (β) cells. This inhibition leads to the closure of potassium channels and the opening of calcium channels[33]. However, none of the studies analyzed demonstrated that sulfonylureas provided neuroprotection[31,33-35].

T2DM and PD are clinically prevalent conditions that negatively affect individuals' quality of life. Thus, it is utmost importance not only to study these diseases in an isolated manner but also to investigate their correlations and interactions. Improvement in insulin levels can regulate the dopaminergic pathway. T2DM and PD as co-morbidity induced in rats using fructose-fed-alloxan model and haloperidol respectively. Long term excess fructose feeding in experimental rats before alloxan injection induces obesity, insulin resistance, and compensatory hyperinsulinemia. This sequence leads to diabetes with hyperglycemia, causing β-cell exhaustion and impaired β-cell function. This hyperglycemia mimics the primary characteristic of human type-2 diabetes[35,36]. Alloxan, a readily available diabetogenic agent, exerts its effect by selective destruction of pancreatic β-cells through generation of Reactive Oxygen Species (ROS), inducing a multiphasic blood glucose response (phase-I, phase-II and phase-III)[36]. The second phase following alloxan administration is characterized by an increase in Blood Glucose Levels (BGL) (first hyperglycemic effect) and a concomitant decrease in plasma insulin levels. The elevated ROS resulting from alloxan administration lead to the rupture of secretory granules and the cell membrane of pancreatic β-cells, causing a severe transient hypoglycemic effect. This mechanism is largely responsible for the mortality associated with the alloxan-induced diabetes model. Phase III then leads to a permanent hyperglycemic state[36].

Haloperidol, a typical antipsychotic, induces catalepsy by blocking postsynaptic dopamine D2 receptors in the mesolimbic system, increasing dopamine turnover, reducing dopamine neurotransmission, and causing marked rigidity. It has a weak blocking effect on cholinergic and β-adrenergic receptors[37-40]. This study aimed to evaluate the effectiveness of gliclazide on changes in motor and cognitive functions in a haloperidol-induced PD model with fructose-fed alloxan-induced diabetes comorbidity in Wistar rats.

MATERIALS AND METHODS

Study protocol approval:

The protocol (CPCSEAC/ARCP/2021-22/01) of the study was approved by of Institutional Animal Ethics Committee (IAEC) of A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar, Gujarat, India.

Selection, procurement and housing of animals:

24 Wistar rats, weighing 150-200 g, were procured from Sun Pharma Research Center, Vadodara, Gujarat, India. The animals were housed under standard conditions following the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and maintained on a 12 h light/dark cycle. They had free access to food, and water was provided ad libitum until the time of experimentation.

Procurement of drugs and chemicals:

Gliclazide, the experimental drug, was procured from Indoco Remedies Ltd., Navi Mumbai. Serenace (haloperidol injection, 5 mg/ml) was obtained from RPG Life Sciences Ltd., and fructose and alloxan were purchased from Sigma-Aldrich, Vadodara, Gujarat, India.

Experimental design and grouping of animals:

24 Wistar rats were divided into 3 groups, with 8 animals in each group[41]. Group I (vehicle control group) received 0.9 % saline orally for 23 d. Group II (model control group) received 20 % w/v fructose in drinking water for the first 14 d, followed by overnight fasting on 14th d. On 15th d, a single dose of freshly prepared 5 % w/v alloxan solution (150 mg/kg) was administered intraperitoneally (IP). 48 h after alloxan administration (on 17th d), the fasting BGL of each rat was measured using a digital glucometer. Rats with a BGL >200 mg/dL were selected for further study (n=6)[36,34,42]. These selected rats were then treated with haloperidol (1 mg/kg/d, IP) for the next 7 d to induce Parkinsonism[43,44]. Group III (gliclazide-treated group) rats (n=6) received the same treatment as group II. Starting on 17th d, in addition to haloperidol, animals in this group also received gliclazide (10 mg/kg/d, *Per os* (P.O)) on a daily basis[45].

Evaluation parameters:

Body weight: The trend in weight gain for animals in all groups was measured using an electronic weighing scale on d 0, 17th d (48 h after alloxan administration), and on 23rd d (the final day of the study)[41,46].

BGL: A One Touch digital glucometer was used to measure the fasting BGL of animals in all groups, with blood collected from the tail vein. Fasting BGL measurements were taken on 0th, 17th, and 23rd d. Both the model control and drug (gliclazide) treatment groups received 20 % w/v fructose in drinking water for the first 14 d, with animals fasted overnight on 14th d. On 15th d, a freshly prepared 5 % w/v alloxan solution (150 mg/kg) was administered IP in the model control and drug treatment groups. After 48 h alloxan administration (17th d), BGL was measured again in all animals. At the end of the study, BGL was reassessed across all groups. In the drug (gliclazide) treatment group, BGL measurements were used to evaluate the antidiabetic effect of gliclazide in the context of PD[36,42].

Motor function tests: Motor functions in all animal groups were evaluated using the bar test, rota rod test, and inclined plane test.

Bar test: Starting on 17th d, following the administration of haloperidol, animals were evaluated daily for motor function using the standard bar test at 0 min and 60 min post-administration. Each animal was placed individually in a translucent plastic box and gently grasped around the shoulders and under the forepaws, then carefully positioned on a wooden bar (3 and 9) cm in height. The time was recorded when the animal removed its paws, and scoring was performed according to the cataleptic score. If an animal remained immobile on the bar for 60 s, it was considered cataleptic[46,47].

Rotarod test: Each day following haloperidol administration, animals were evaluated for motor function using the rotarod apparatus at 0 min and 60 min post-administration. Motor coordination was assessed by testing each animal's ability to remain on a rotating rod (20-25) rpm. The fall-off time for each animal in each group was recorded and documented as a percentage decrease in fall-off time[47,48].

Inclined plane: Motor function in all animals was also evaluated using an inclined plane/sliding apparatus 0 min and 60 min after haloperidol administration (from 17th d to 23rd d). Prior to the actual experiment, each rat received training. Each rat from each group was placed individually at the bottom of the inclined plane set at a 45° angle, and the time taken to reach the top was recorded. Animals that failed to reach the top within 20 s were considered cataleptic[49].

Cognitive function tests: Cognitive functions in all groups were evaluated using the alteration method in the Y-maze and the Morris water test on the day following haloperidol administration, between 8 AM and 12 PM, to avoid circadian errors.

Y-maze test: Cognitive functions in all animals were evaluated daily using the Y-maze alteration test on the day following haloperidol administration. Each rat was placed in the center of the maze and allowed to move

freely for 5 min, with one of the arms closed. In this study, the 'B' arm of the Y-maze was designated as the main arm for exploration. The series of arm entries, including possible returns to the same arm, were recorded visually. The number of alteration behaviors and the total number of entries were documented over the 5 min period until 23rd d. Alterations were defined as the number of arm entries into all three arms consecutively; for instance, if the animal made the following arm entries such as ABC, BCA, or CAB. The percentage of alteration was calculated using the formula

Percentage alteration=(number of alterations/total number of entries-2×100

Here, alterations are defined as the total number of arm entries minus two. The percentage of alteration represents the ratio of actual alterations to possible alterations[43,49].

Morris water test: Each day following the administration of haloperidol, animals were evaluated for cognitive function using the Morris water test. A circular tank (2 m in diameter) filled with water was used for this test. At the beginning of each trial, the animals were placed in the water facing the side walls of the pool, with a different starting position for each trial. They quickly learned to swim and locate the correct location (a hidden platform submerged in the water), indicated by a decrease in escape latency. Each animal was individually placed in a circular water filled tank, and its swimming activity was monitored visually. The time taken to find the platform (in seconds) was recorded. Each rat was allowed 60 s to find the hidden platform. If a rat was unable to find the platform within 60 s, it was gently placed on it and allowed to remain there for 10 s[43].

Statistical analysis:

All data were expressed as Mean±Standard Error of the Mean (SEM) (n=6). Statistical significance for parametric data was tested using one-way Analysis of Variance (ANOVA) followed by Dunnett's test, while non-parametric data were analyzed with the Wilcoxon test in GraphPad Instat 9.0. A p-value of <0.05 was considered significant for all analyses, indicating a 95 % confidence level.

RESULTS AND DISCUSSION

PD is the second most prevalent neurodegenerative disease worldwide. T2DM is one of the etiological factors that increases the risk of PD development and progression. Recently, awareness of the link between T2DM and PD has also increased. In the present investigation, a co-model of diabetes and PD in Wistar rats was used to evaluate the effectiveness of gliclazide. To induce diabetes in the model control and drug-treated groups, animals received a 20 % w/v fructose solution in their drinking water for 14 d, followed by a single IP dose of alloxan (150 mg/kg) on 15th d[42].

Several studies in rats confirm that an excess intake of dietary fructose increases lipogenesis, leading to fat buildup, body weight gain, and obesity[50-54]. Other possible mechanisms include a low concentration of the fructose transporter Glucose transporter 5 (GLUT5), which neither stimulates insulin secretion from pancreatic beta cells nor leptin secretion[55-57].

Insulin not only regulates BGL but also controls body adiposity by acting on the Central Nervous System (CNS) to reduce food intake. Disruption of the insulin signaling pathway or reduced insulin transport in the CNS results in weight gain and obesity[57]. Table 1 shows the trend in weight gain of Wistar rats on 0th d and 17th d. Rats in the model control group (96.67±3.57) and drug (gliclazide) treated group (90.83±4.9), which received a 20 % fructose solution in drinking water for two weeks followed by an IP injection of alloxan, showed a significant increase in weight gain ($p<0.0001$) compared to the vehicle group (31.66±4.94).Weight gain from 17th d to the last day of the study (23rd d) in the vehicle, model control, and drug treated groups was 18.33±2.78, 20±3.27, and 8.33±2.12, respectively. This trend in weight gain for the model control group was not statistically significant compared to the vehicle group. However, the weight gain in the drug treated group was found to be significant ($p<0.05$) when compared to both the vehicle and model control groups.

TABLE 1: CHANGE IN BODY WEIGHT (gm)

Group	Vehicle control	Model control	Drug control
0th d to 17th d	31.66±4.94	**96.66±3.57	**90.83±4.9
17th d to 23rd d	18.33±2.78	**20±3.27	*8.33±2.12

Note: Data are expressed as mean±SEM, n=6, **p<0.0001, when compared to change in body weight at 17th d after alloxan administration in model control group and drug treated group with vehicle control group and at the 23rd d *p<0.05, when compared to model control group with drug treated group

Excessive fructose intake induces insulin resistance and obesity in experimental animals, leading to compensatory hyperinsulinemia. These mechanisms cause β-cell exhaustion, resulting in impaired β-cell function[35,36]. Alloxan is a readily available diabetogenic agent that exerts its effect by selectively destroying pancreatic β-cells through the generation of ROS. Alloxan induces a multiphasic BGL response, described in phases such as phase I, phase II, and phase III[35]. The second phase after alloxan administration is characterized by increased BGL (first hyperglycemic effect) and a concomitant decrease in plasma insulin levels. The increased ROS levels due to alloxan administration induce the rupture of secretory granules and the cell membrane of pancreatic β-cells, resulting in a severe transient hypoglycemic effect. This mechanism is largely responsible for the mortality associated with the alloxan-induced diabetes model[35]. In this study, no mortality was observed, which may be due to a modification or control of this mechanism. 20 % w/v fructose in drinking water for 14 d followed by single dose of freshly prepared 5 % w/v solution of alloxan induced diabetes in animals was demonstrated by fasting BGL assessment (vehicle group: 3.16±1.86; model control: 117.5±4.11; drug control: 120.5±4.49). However, the change in BGL was not found to be significant. These animals had received haloperidol (1 mg/kg/d IP) as well. Comparing the change in BGL in model control group (10.33±4.72) with drug (gliclazide) treated group (95.16±10.43) the difference was found to be highly significant ($p<0.0001$) (Table 2). In present study use of fructose fed alloxan model had induced better hyperglycemia effect and also reduce risk of mortality in animals. Significant increase in BGL (>200 mg/dL) level in rats, suggesting diabetes induction.

Dopaminergic neuron deficiency and increased dopamine turnover are key factors in the development of PD[55]. Haloperidol, a typical antipsychotic agent, produces its effects by blocking dopaminergic receptors, and marked rigidity associated with haloperidol administration has been observed[57]. In the present study, PD induced by haloperidol was associated with motor deficits and cognitive impairment[35]. Gliclazide, a sulfonylurea-type antidiabetic agent, exerts its insulin secretagogue action by acting on the K^+ ATP channels[56]. Our findings indicate that gliclazide improves haloperidol-induced PD in rats by enhancing motor and cognitive functions compared to the model control group. A dose of gliclazide (10 mg/kg/d) prevented movement deficits in the drug treatment group induced by disease induction. gliclazide produced a significant effect against PD by preventing body weight gain, increasing fall-off time, reducing the time required to reach the top of the inclined plane, shortening the latency to locate the hidden platform in the Morris water maze, increasing percentage alteration behavior in the Y-maze, and decreasing cataleptic scores in the bar test.

Statistical analysis of the rotarod test for motor function revealed that rigidity and catalepsy in the model control group (64.83±12.4) increased from 17th d to 23rd d, showing a significant difference ($p<0.05$) compared to the vehicle group (23.16±4.81). However, this significant difference was not observed between the model control group and the drug treated group (39.16±7.69). Table 3 shows that the motor function deficit induced by haloperidol from 17th d to 23rd d was significantly higher ($p<0.0001$) in the model control group (4.66±0.61) compared to the vehicle group (0±0). The gliclazide-treated group (2.33±0.76), however, showed a significant improvement in motor function ($p<0.01$) compared to the model control group.

The results of the bar test indicate that haloperidol-induced rigidity and catalepsy significantly increased in the model control group compared to the drug treated group, with scores of 0.16±0.10 and 0.44±0.18, respectively ($p<0.0001$). Furthermore, this difference was not significant when comparing the model control group to the vehicle group (0±0) (Table 3). The results of the Morris water test are depicted (Table 4). Haloperidol-induced PD, which resulted in cognitive impairment, was noted in the model control group with a score of 2.5±0.56, compared to the vehicle group (2.83±0.7). Improvement in cognitive function was evidenced by a decrease in the latency time required to explore the hidden platform, with the gliclazide treated group showing a score of 1.83±0.6 compared to the model control group. However, the data from the Morris water test were not found to be significant in any of the groups. Statistical analysis revealed that the administration of haloperidol produced a significant decrease ($p<0.001$) in percentage alteration behavior in the model control group (41.84±3.77) compared to the vehicle group (68.38±5.58) on 23rd d. However, the gliclazide-treated group (62.80±3.15) showed a significant increase ($p<0.005$) in percentage alteration behavior compared to the model control group (Table 4). These effects may be attributed to improvements in insulin levels, which impact the dopaminergic pathway. Although the positive effects on motor and cognitive function were evident, they were not sufficient to

restore all symptoms of motor coordination to baseline levels. Therefore, studying the interactions between these factors may provide deeper insights into the mechanisms involved in PD and DM. Taken together, our findings, in accordance with previous research, confirm the role of gliclazide in improving motor function in PD. Furthermore, gliclazide appears to counteract the effects of haloperidol and the fructose-fed alloxan regimen on motor activity. In light of these results, gliclazide seems to be protective and a promising candidate for clinical trials in individuals using anti-diabetic drugs, particularly those in the early stages of PD. However, additional preclinical studies are needed to confirm this pharmacological effect

TABLE 2: EFFECT OF GLICLAZIDE ON CHANGE IN BGL (mg/dl)

Group	Vehicle control	Model control	Drug control
0^{th} d to 17^{th} d	3.166±1.86	**117.5±4.113	**120.5±4.49
17^{th} d to 23^{rd} d	5.166±2.12	*10.33±4.72	$^{\#\#}$95.16±10.43

Note: Data are expressed as mean±SEM, n=6, change in BGL between 0^{th} d to 17^{th} d after alloxan administration, **p<0.0001 when compared to model control group and drug treated group with vehicle control group, at the end of the study period 23^{rd} day. $^{\#\#}$p<0.0001 when compared to drug treated group with vehicle control group and *p<0.0001 when compared to model control group with drug control group by using one way ANOVA followed by Dunnet's test

TABLE 3: EFFECT OF GLICLAZIDE ON MOTOR FUNCTIONS

Group	Vehicle control	Model control	Drug control
Rotarod test (change in fall-off time)	23.16±4.81	*64.83±12.4	39.16±7.69
Inclined plane test (change in time to reach at the top)	0±0	**4.66±0.61	$^{\#}$2.33±0.76
Bar test (change in catalepy score)	0±0	0.16±0.10	**0.44±0.18

Note: Data are expressed as mean±SEM, n=6, in rotarod test *p<0.05 when compared to model control group with vehicle control group by one way ANOVA followed by Dunnet's test, in inclined plane test **p<0.0001 when compared to model control group with vehicle control group; $^{\#}$p<0.05 when compared to model control group with drug treated group by one way ANOVA followed by Dunnet's test and in bar test, **p<0.0001 when compared to model control group with drug treated

TABLE 4: EFFECT OF GLICLAZIDE ON COGNITIVE FUNCTION USING MORRIS WATER TEST AND Y-MAZE TEST

Group	Vehicle control	Model control	Drug control
Morris water test (change in latency time)	2.83±0.74	2.5±0.56	1.83±0.6
Y-maze test (% alteration behaviour)	68.38±5.58	**41.84±3.77	*62.80±3.15

Note: Data are expressed as mean± SEM, n=6, one way ANOVA followed by Dunnet's test for Morris water test, data was expressed as mean±SEM, n=6, **p<0.005 and alteration behaviour in Y-maze test when compared to vehicle control group with model control group and *p<0.005 when compared to drug treated group with model control group by one way ANOVA followed by Dunnet's test

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Author's contributions:

Musaratafrin Saiyed contributed to conceptualization, methodology, visualization, writing-original draft, writing-review and editing, and project administration. Punam Sachdeva was involved in conceptualization, methodology, visualization, writing-review and editing, and supervision. Neha Sharma contributed to software, investigation, and writing-review and editing, and Kruti Sharma worked on software, writing-original draft, and writing-review and editing.

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Conflict of interest:

The authors declared no conflict of interests.

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