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Research Article

Effect of PPAR α/γ agonist on Behavioural Alterations in 6-OHDA induced Parkinson Disease

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Abstract

AIM- The aim of present research work aimed to investigate the neuroprotective potential of saroglitazor in experimental animal model of neurodegenerative disease. **MATERIAL & METHODS-** Sixty Male Wistar albino rats (150-200 gm) were obtained from the Central Animal House of Pharmaceutical Sciences, India. The tablets of 4 mg Saroglitazor (SG), were weighed and finely powdered and then transferred into a 10-ml calibrated flask, dissolved in 4 ml sterile saline solution (0.9% NaCl), swirled and sonicated for 5 min, completed to volume with saline, and shaken well for 15 min immediately before administration. For the post operative care, Povidone-iodine was applied to all the animals for one week after surgery and gentamycin (7 mg/kg) were given to all animals 24 hourly for 2 days. The Rota rod unit consists of a rotating rod, 48 mm in diameter, which was divided into four parts by compartmentalization to permit the testing of four rats at a time. **RESULTS-** DC group showed marked ($p < 0.0001$) decline in fall off time as compared to NC group. On the other hand, SG-1, SG-3 and SG-10 groups showed dose dependent remarkable ($p < 0.005$, $p < 0.0001$, respectively) rise in fall off time when compared to DC group. SG-1, SG-3 and SG-10 groups showed drastic ($p < 0.0001$) growth in forehand adjusting steps and noticeable ($p < 0.001$) increment in backhand adjusting steps with exception of non significant rise with SG-1 group, when compared to DC group. **CONCLUSION-** In brief, for the first time we report that novel dual PPAR α/γ agonist, SG inhibited 6-OHDA-induced dopaminergic Neurodegeneration and mitigated behavioral alterations in rat model of PD.

Keywords: Dopaminergic Neurodegeneration, Saroglitazor, Parkinson's disease, Substantia nigra pars, Compacta region

INTRODUCTION

Historically, Parkinson's disease (PD) was first defined by James Parkinson in 1817. PD is a neurodegenerative disorder that negatively affects one's ability to move. The distinctive features of PD include tremors, akinesia, rigidity, postural instability, and gait disturbances. Moreover, pathological characteristics of a parkinsonian brain include significant degeneration of striatal dopaminergic neurons in substantia nigra pars compacta region. Thus, striatal neurodegenerative process leads to a drop in dopamine level, which causes motor imbalance followed by non-motor symptoms ultimately leading to poor quality of life of the patients and their caretakers. Currently, available treatment options only alleviate the symptoms of PD. The non-availability of safe and effective therapy poses a formidable challenge to coping with the disease progression in the lives of parkinsonian patients. This stimulates researchers across the globe to find and develop effective and safe treatment options that can enhance the quality of life of PD patients and their caretakers (Boggio *et al.*, 2006). It is projected to increase by five to ten folds in the elderly population of more than 60 years of age. Simultaneously, the prevalence of PD is also increasing with age. According to the outcome of several meta-analyses, an increase in prevalence from less than one percent to four and two percent was noted in men and women, respectively. These

data explain the higher progression of the prevalence rate in men compared to women (Chang *et al.*, 1999). Such dramatic differences in the prevalence of PD amongst males and females may be due to various reasons, such as occupational exposures, neuroprotective actions of oestrogens in females, and other genetic factors (Elbaz *et al.*, 2016). The aim of present research work aimed to investigate the neuroprotective potential of saroglitazor in experimental animal model of neurodegenerative disease.

MATERIALS AND METHODS

ANIMALS

Sixty Male Wistar albino rats (150-200 gm) were obtained from the Central Animal House of Pharmaceutical Sciences, India. The animals were housed at room temperature ($25 \pm 1^\circ\text{C}$) with 50-55% relative humidity, 12 h light/12 h dark cycle (lights off from 19:30- 07:30), and given food pellets and water *ad libitum*. The study was approved and conducted as per the norms of the Institutional Animal Ethics Committee. For the present study, a total of 60 animals were distributed into five groups of 6 animals each and allowed to acclimatize for one week before the experiments to avoid non-specific stress.

TREATMENTS

The tablets of 4 mg Saroglitazor (SG), were weighed and finely

powdered and then transferred into a 10-ml calibrated flask, dissolved in 4 ml sterile saline solution (0.9% NaCl), swirled and sonicated for 5 min, completed to volume with saline, and shaken well for 15 min immediately before administration. The effect of the repeated systemic oral administration of SG on 6-OHDA-induced behavioral, neurochemical and pathological deficits and dopaminergic cell death was investigated by administering SG (1 mg/kg/day, 3 mg/kg/day, 10 mg/kg/day) or its vehicle (sterile saline solution-0.9% NaCl) during 21 consecutive days by oral route.

EXPERIMENTAL PROTOCOL

Experimental groups

Group I: Sham-operated + Normal saline

Group II: Intrastriatal administration of 6-OHDA (20 µg/2µl) + Normal saline

Group III: Intrastriatal administration of 6-OHDA (20 µg/2µl) + SG (1 mg/kg, p.o.)

Group IV: Intrastriatal administration of 6-OHDA (20 µg/2µl) + SG (3 mg/kg, p.o.)

Group V: Intrastriatal administration of 6-OHDA (20 µg/2µl) + SG (10 mg/kg, p.o.)

Postoperative care

Recovery of anesthesia took approximately 4-5 h. The rats were kept in a well-ventilated room at 25 ± 3 °C in individual cages. Food and water were kept inside the cages for the first week so that animals could easily access them without any physical trauma due to overhead surgery. Then the animals were treated normally; food, water, and the bedding of the cages were changed every day as usual. Povidone-iodine was applied to all the animals for one week after surgery and gentamycin (7 mg/kg) were given to all animals 24 hourly for 2 days.

Behavioral testing

Apomorphine-induced circling behavior

The effect of 6-OHDA and protection by SG (1 mg/kg, 3 mg/kg, and 10 mg/kg) was evaluated on apomorphine-induced rotations in lesioned rats. The animals were given 0.5 mg/kg apomorphine (in ascorbic acid-saline) subcutaneously to monitor contra-lateral rotations. Net rotations toward the contralateral side were collected at five minutes intervals. The rats were checked and monitored for any basal level of contra-lateral rotations before surgery (Ahmad *et al.*, 2005).

Rota-rod performance

Rota rod apparatus (Instruments & Chemicals Pvt. Ltd., Ambala City, India) was used to evaluate the muscular coordination after 21 days of 6-OHDA injection. The Rota rod unit consists of a rotating rod, 48 mm in diameter, which was divided into four parts by compartmentalization to permit the testing of four rats at a time. After twice-daily training for 2 successive days (speed 8 RPM on the first day and 10 RPM on the second day), the rotational speed of the test was increased to 15 RPM on the third day in a test session (Rozas *et al.*, 1998).

Total locomotor activity

Total locomotor activity was monitored using a photoactometer (Instrument & Chemical Pvt Ltd, MT, Ambala City, India). Animals were individually placed in a photoactometer for the first 3 min for acclimatization before actual recording of activity for the next 5 min. The locomotor

activity was expressed in terms of total photo beam counts/5 min/animal. The chamber was swabbed with 10% ethanol every time to avoid interference due to the animal odors (Jung *et al.*, 2006).

Stepping test

The Rats were held with one hand by the experimenter fixing the hind limbs (slightly raising the torso) and with the other hand, fixing the forelimb that was not to be monitored. In this way, the other forepaw had to bear the weight. The rats were moved slowly sideways in both forehand and backhand directions (Kalonias *et al.*, 2010).

Cylinder test

The cylinder test assesses the spontaneous forelimb lateralization, taking advantage of the natural exploratory instinct of rodents to a new environment (Schallert *et al.*, 2000). Rats were placed individually inside a glass cylinder (diameter 19 cm, height 20 cm). The number of wall touches (contacts with fully extended digits) executed independently with the ipsilateral and the contralateral forelimb were counted. Simultaneous paw touches were excluded from the analysis.

Elevated body swing test

A swing was recorded whenever the animal moved its head out of the vertical axis to either side. Before attempting another swing, the animal must return to the vertical position for the next swing to be counted. When the animal did not commence swing behavior when it was elevated for more than 5 sec, a gentle pinch to the tail induced the behavior. Swings were recorded using a hand counter. The total number of swings made to each side was divided by the overall total number of swings made to both sides to get percentages of left and right swings. The criterion for biased swing behavior was set at 70 % or higher (Borlongan and Sanberg, 1995).

Bar test

Catalepsy was evaluated in the bar test on the 22nd consecutive days after the surgery. The apparatus was made of wood (23 cm long 10.5 cm wide 9 cm high) with a horizontal bar (0.4 cm diameter 23 cm long) suspended 9 cm above the floor, similar to that reported in the literature. Catalepsy was evaluated by measuring the mean time spent by a rat to climb over the bar after being laid across it with its hind limbs on the floor (Wang *et al.*, 2009; Sy *et al.*, 2010; Hsu *et al.*, 2015).

Open field test

Rats were assessed individually for 5 min, while four parameters were analysed: (i) latency to start the movement (time to leave the inner circle, in s), (ii) locomotion frequency (number of squares crossed with four paws), (iii) rearing frequency (number of times the animal stood on their hind paws) and (iv) immobility time (lack of movement during testing, in s). The apparatus was cleaned with 5 % ethanol solution before behavioral testing to eliminate possible bias due to odors left by the previous rat (Breidert *et al.*, 2002; Bernardi and Neto, 1979).

Elevated plus-maze

The elevated plus-maze consisted of two open arms (50×10×0.75 cm) and two enclosed arms (50×10×40 cm), arranged such that two pairs of identical arms were opposite to each other. Arms emerged from a central platform (10×10 cm), and the entire apparatus was raised to a height of 50 cm above floor level. Experiments were performed under dim light conditions. At the beginning of the test, the rat was placed on the central platform facing an open arm. After each 5 min test, the maze was carefully cleaned up with a wet towel.

Anxiety was evaluated through the following behavioral parameters: % open arm entries (% open arm entries: open entries/ total entries $\times$ 100) and percent time on open arms (% open time) (Dawson and Tricklebank, 1995)

Statistical analysis

Statistical analysis was carried out using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). All the data are presented as mean $\pm$ S.E.M. The significance of difference of different parameters determined by One-way Analysis of Variance (ANOVA) followed by Tukey's test. A value of $p < 0.05$ was considered as statistically significant.

RESULTS

APOMORPHINE-INDUCED CIRCLING BEHAVIOR

ROTA-ROD PERFORMANCE

Results depicted in Table 1 clearly indicated the negative impact of 6-OHDA. As, there was no significant difference in fall off time detected between the animals of all five groups, which was evidently notable after 6-OHDA lesion. DC group showed marked ($p < 0.0001$) decline in fall off time as compared to NC group. On the other hand, SG-1, SG-3 and SG-10 groups showed dose dependent remarkable ($p < 0.005$, $p < 0.0001$, respectively) rise in fall off time when compared to DC group.

TOTAL LOCOMOTOR ACTIVITY

Negative effect of 6-OHDA was also evident from locomotor test, as shown in Table, before 6-OHDA, there was no significant difference found between groups in terms of photo beam counts. The same were remarkably ($p < 0.0001$) lesser in DC group as compared to NC group. With exception to SG-1 group, SG-3 ($p < 0.005$) and SG-10 ($p < 0.001$) group showed dose dependent significant boost in photo beam counts when compared to DC group.

STEPPING TEST

Contra lateral forehand and backhand adjusting steps were noticeably ($p < 0.0001$) declined in DC group as compared to NC group. SG-1, SG-3 and SG-10 groups showed drastic ($p < 0.0001$) growth in forehand adjusting steps and noticeable ($p < 0.001$) increment in backhand adjusting steps with exception of non significant rise with SG-1 group, when compared to DC group.

CYLINDER TEST

Profound detrimental effect of 6-OHDA was evident after 21 days of 6-OHDA lesion. There were drastic ($p < 0.0001$) fall down in % contra lateral touches in DC group observed as compared to NC group. While, dose dependent marked elevation in % contra lateral touches were seen in SG-1 (non significant rise), SG-3 ($p < 0.005$) and SG-10 ($p < 0.001$) groups when compared to DC group

ELEVATED BODY SWING TEST

Table showed significantly ($p < 0.0001$) higher percentage of left side swings in DC group compared to NC group. However, treatment groups (SG- 1, SG-3 and SG-10) showed dose dependent prominent ($p < 0.001$ and $p < 0.0001$, respectively) decrement in percentage of left side swings when compared to DC group.

GRIP STRENGTH

Grip strength score was found to be reduced strikingly in DC group as compared to NC group. However, it was improved dramatically in SG-1, SG-3 and SG-10 ($p < 0.005$) groups when

compared to DC group.

BAR TEST

Rise in bar crossing latency was significantly higher in DC group compared to NC group. Interestingly, the same was decreased dose dependently and profoundly in SG-1 (insignificant decline), SG-3 ($p < 0.001$) and SG-10 ($p < 0.0001$) groups when compared to DC group.

DISCUSSION

To evaluate the efficacy of SG, 6-OHDA induced rat model of PD was used. In which, neurotoxin 6-OHDA is directly administered into the striatal region of rat brain. Following that, it concentrates into cytosol, destruct DA and non-dopaminergic transporters and generates H₂O₂, ROS, RNS and quinines by auto-oxidation (Suliman *et al.*, 2003). These destructive mechanisms are responsible for the death of DA neurons over a period of 1-3 weeks. Both DA transporters and noradrenergic transporters are negatively affected by detrimental effects of 6-OHDA (Issa *et al.*, 2018) that is responsible for attenuation in DA content and other catecholamine.

Apomorphine-induced contra lateral rotation in 6-OHDA-lesioned rats is a trustworthy indication for the nigrostriatal DA diminution. Contralateral rotational behavior due to apomorphine is only observed when the injury is absolute or nearly absolute whereas, the slightly injured rats do not rotate significantly (Przedborski *et al.*, 1995). We report that the treatment with SG attenuated the damage of striatal DA neurons induced by 6-OHDA and significantly decreased the Apomorphine induced rotation in rats. The study revealed restoration of injury in striatal region by SG treatment. Our results are in well harmony with other studies, which have described reduction in Apomorphine induced rotational behavior following exposure to various treatments in experimental animals (Jin *et al.*, 2008; Khatri, and Juvekar, 2016).

Biased swinging behaviour of rat contralateral to lesioned side is a result of imbalanced DA levels in the left and right sides of brain. Mechanism that explicates this behaviour may involve stressor effect such as hanging rats from the base of their tail from 2 cm above the surface followed by tail pinching. As described in the results, rats of DC group showed higher number of % left swing compared to NC group and SG treatments reduced this behavior (Borlongan and Sanberg, 1995; Haghdoust-Yazdi *et al.*, 2011).

The behavioral changes are clear indicators of degree of neuronal dysfunction. In the Rota-rod task, animals are allowed to stroll on a rotating rod and the evaluation is done on the basis of how long animal is capable to be on the rotating rod as a function of its speed and performance is recorded as duration in seconds. The ample of information has been obtained regarding the qualitative aspects of walking movements and motor harmonization (Whishaw *et al.*, 2008). As stated by our results, motor harmonization skill was decreased in 6-OHDA-lesioned group and elevated significantly by the treatment with SG. Others have also reported that motor imbalance in parkinsonian rats have been equilibrated by antioxidant treatment (Chaturvedi *et al.*, 2006; Jin *et al.*, 2008).

The stepping test is proposed to screen motor initiation deficits in the forelimbs, similar to limb akinesia and gait problems in PD patients (Schallert, Norton and Jones, 1992). According to our findings, SG treatment significantly reduced the motor deficits due to 6-OHDA administration, are in well accordance

with earlier study which illustrates the shielding effect of anti-oxidant and anti-inflammatory substance such as HMG Co-A reductase inhibitors against 6-OHDA-induced akinesia.

Catalepsy is a characteristic symptom of PD. Neuropharmacological mechanism responsible for cataleptic behavior of rats in DC group is probably due to marked destruction of DA neurons by 6-OHDA and loss of DA receptors in nigrostriatal region. Previously, authors have reported the reversal of MPTP-induced cataleptic behavior with ceftriaxone treatments in rats (Hsu *et al.*, 2015). Our results are in well harmony with the earlier reports as, rats of SG treated group exhibited significantly lesser catalepsy compared to DC group. This may be due to protective role of SG from 6-OHDA by inhibition of oxidative stress and neuroinflammation that leads to apoptosis of DA neurons in the striatum.

Grip strength is a simple widely used test of motor function and coordination assessment. Healthy rats spontaneously show climbing activity on to the metal string tied above the surface, which requires grip strength as well as coordination of muscle movements. Our results are in accordance with the earlier studies where in 6-OHDA significantly caused motor imbalance and reduced grip strength which was restored by curcumin treatment (Khuwaja *et al.*, 2011). In this study, SG treatment was effective in improving grip strength compared to DC group. Possible reason behind this may be DA neuron

protective role of SG and inhibition of oxidative stress induced neuronal cell death.

Quantification of exploratory and general locomotor activity was evaluated by this experiment. Previous authors have reported that curcumin (Khatri and Juvekar, 2016), Schinus terebinthifolius (Shalavadi *et al.*, 2012) and lycopene (Prema *et al.*, 2015) were found effective in reducing the motor deficits in open field paradigm. Likewise, in our study also SG treatment was effective in improvement of overall open field test parameters such as locomotion frequency, rearing frequency and immobility time (a measure of anxiety behaviour). This indicates protective role of SG in reversal of motor imbalance and anxiety behaviour in novel environment.

CONCLUSION

In brief, for the first time we report that novel dual PPAR α/γ agonist, SG inhibited 6-OHDA-induced dopaminergic neurodegeneration and mitigated behavioral alterations in rat model of PD. Moreover, neuroprotective efficacy of SG is attributed to various shielding mechanisms such as, reduction in ROS/RNS concentrations via increasing activities of protective endogenous antioxidant enzymatic defense, suppression neuroinflammation by decreasing inflammatory markers. Thus, it is proved that SG possess strong anti-parkinsonian efficacy in rat model of PD.

Table 1: Effect of saroglitazar on 6-OHDA-induced behavioral alterations

Treatment Group	Apomorphine induced rotation	Rota rod {Fall off time (sec.)}		Photoactometer		Stepping test	
		Before 6-OHDA	After 6-OHDA	Before 6-OHDA	After 6-OHDA	Forehand steps	Backhand steps
NC	0.583±0.19	136.8± 2.91	133.1± 1.07	226± 9.53	220.4± 10.21	21.3± 0.78	21.3±1.15
DC	16.6±0.75***	130.4± 1.78	40.21±2.56***	237.1± 13.12	89.8±2.01**	7.42± 0.39***	11.5±1.13*
SG-1	12.7±0.55**	131.4± 1.98	56.67± 0.94**	131.4± 31.51	137.3± 1.16**	9.67± 1.25**	15.7±1.39**
SG-3	9.17±1.17***	125.9± 5.84	75.42± 0.89**	252.1± 17.86	151.6± 5.43**	13.1± 1.17**	17.1±1.03**
SG-10	8.67±0.75***	135.9± 8.49	104.9± 0.88***	249.4± 8.02	173.7± 5.95***	13.9± 1.08***	17.1±1.58**

Table No. 2: Effect of saroglitazar on 6-OHDA-induced behavioral alterations

Group	Cylinder Test		Elevated swing test	Grip Strength	Bar Test
	Before 6-OHDA	After 6-OHDA			
NC	17.5 ± 1.89	21.3 ± 1.22	58.5 ± 1.94	4.33 ± 0.22	1.33 ± 0.32
DC	17.3 ± 1.60	10.4 ± 1.14***	77.3 ± 1.95**	2.08 ± 0.26**	7.42 ± 0.81***
SG-1	18.8 ± 1.26	15.3 ± 1.48**	66.2 ± 2.71*	2.67 ± 0.32**	5.92 ± 0.76**
SG-3	18.7 ± 1.34	14.0 ± 1.71**	62.9 ± 3.26**	3.17 ± 0.48**	4.17 ± 0.51**
SG-10	19.7 ± 1.28	11.7 ± 1.11***	56.7 ± 2.39***	3.50 ± 0.44**	2.83 ± 0.44***

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