Niger. J. Physiol. Sci. 35 (December 2020): 203 - 208
www.njps.physiologicalsociety.com

Niger. J. Physiol. Sci.

Research Article

Vinpocetine Prevents Haloperidol-Induced Cognitive and Working Memory Deficits Through Attenuation of Oxidative and Nitrosative Stress in Mice

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Summary: There is a strong interplay between central mechanisms regulating emotional and cataleptic states similar to that observed in Parkinson's disease (PD). Several drugs including haloperidol have been implicated in the aetiology of PD. However, prolong treatment of PD patients with current available drugs induced dyskinesia, hence, the need for better treatment options. Vinpocetine, a derivative of the alkaloid vincamine used as a dietary supplement to enhance cognition and memory. Several studies have reported therapeutic benefit of vinpocetine in various disease conditions. Thus, this study sought to investigate the protective effect of vinpocetine against haloperidol-induced catalepsy in mice. Vinpocetine (5, 10 or 20 mg/kg, p.o.) was administered 1 h after haloperidol injection for 21 consecutive days. Effect on motor coordination, depressive-like behaviour and working memory were assessed with rotarod, forced swim test (FST) and Y-maze test (YMT), respectively. Brains were collected on day 21 for biochemical estimation of nitrosative and oxidative stress parameters. Vinpocetine (10 or 20 mg/kg, p.o.) significantly reversed haloperidol-induced motor deficit in rotarod test and open field test and reduced the duration of catalepsy during acute and subchronic catalepsy tests as compared to trihexylphenidyl but failed to reverse haloperidol-induced memory deficit in the Y-maze test. Haloperidol-induced increase in malondialdehyde and nitrite generation as well as deficits in antioxidant enzymes activities were attenuated by subchronic administration of vinpocetine. These findings suggest that vinpocetine protects against haloperidol-induced catalepsy and motor deficits through attenuation of oxidative/nitrosative stress.

Keywords*: catalepsy; haloperidol; memory; oxidative stress; Parkinsonism; Y-maze test*

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Manuscript received: March 2020; Revised version accepted: December, 2020

INTRODUCTION

Parkinson's disease (PD) is the second most common age-related neurodegenerative progressive disorder and affects basal ganglia circuitry. It is characterized by extensive dopamine neuron degeneration in the substantia nigra pars compacta (SNpc) exerting an impact on the striatum as well as on target cortical and limbic areas (Björklund and Dunnett, 2007). It was estimated that over five million people worldwide have PD (Fahn and Przedborski, 2008). There is substantial geographic and ethnic variability in the prevalence and incidence in Africa with generally lower rate reported (Okubadejo *et al*., 2006). Most obvious symptoms early in the course of the disease are movement-related, such as resting tremor, muscular rigidity, bradykinesia and postural imbalance (Lotharius and Brundin, 2002; Olanow, 2007). The mechanism for dopaminergic neuronal degeneration in PD is not completely clear, but it is believed that oxidative and nitrosative stress play important role during the disease pathogenesis. This notion is supported by findings on an increase of several indices of oxidative and nitrosative stress (overproduction of nitric oxide (·NO), often complicated by simultaneous production of superoxide anions, which results in the formation of peroxynitrite and other reactive nitrogen species) in PD patients (Khan *et al*., 2012; Nakamura and Lipton, 2011; Polydoro *et al*., 2004). The selective dopaminergic degeneration in PD suggests that generation of oxidative stress associated with dopamine metabolism is an important contributor (Tsang and Chung, 2009). In addition, postmortem studies of brains from PD victims suggest that oxidative stress plays an important role in the degeneration of dopaminergic neurons in the SNpc (Fahn and Cohen, 1992).

The discovery that administration of haloperidol to rodents led to a transient Parkinsonian-like state was rapidly followed by the key discovery that these symptoms were reversed by the administration of L-DOPA (Duty and Jenner, 2011; Knol *et al*., 2012). Haloperidol works by antagonizing dopamine D_2 and, to a lesser extent, D_1 receptors in medium spiny neurons that comprise the indirect and direct pathways of the motor circuit respectively. The resultant block of striatal dopamine transmission results in abnormal downstream firing within the basal ganglia circuits that is manifest as symptoms of muscle rigidity and catalepsy within 60 min of haloperidol injection (Duty and Jenner, 2011). Moreover, acute administration of haloperidol has been shown to reduce the striatal content of dopamine, noradrenaline and 5-HT (Kulkarni *et al*., 2009). Haloperidol induces a six-fold increase in levels of reactive oxygen species (ROS), which are generated from mitochondria but not from the

metabolism of catecholamines by monoamine oxidases (Sagara, 1998).

Vinpocetine (marketed as Cognitol®), a derivative of the alkaloid vincamine isolated from periwinkle plant, has been clinically used in many countries for treatment of cerebrovascular disorders such as stroke and dementia for more than 30 years. Currently, vinpocetine is also available in the market as a dietary supplement to enhance cognition and memory. Due to its excellent safety profile, increasing efforts have been put into exploring the novel therapeutic effects and mechanism of actions of vinpocetine in various cell types and disease models. (Zhang *et al*., 2018). Earlier studies on anti-inflammatory (Zhang *et al*., 2014; Wu *et al*., 2017), vascular remodeling and anti-atherosclerosis (Cai *et al*., 2012) action of vinpocetine have been reported. We earlier showed that vinpocetine prevented paraquat-induced motor deficits, memory impairment, oxidative stress and neuroinflammation through enhancement of antioxidant defense system and inhibition of neuroinflammatory cytokine in mice (Ishola *et al*., 2018). Thus, this study sought to evaluate the protective effect of vinpocetine on haloperidol-induced Parkinsonism in mice. Findings from this study may facilitate the repositioning of vinpocetine in the treatment of PD in humans.

MATERIALS AND METHODS

Drugs and chemicals: Haloperidol 4-[4-(4-chlorophenyl)-4-hydroxypiperidinol]-4-fluorobutyrophenone, sodium hydroxide, Triton x-100, sodium chloride (NaCl), sodium nitrate (NaNO2), sulphanilamide, napthaylamine diamine dihydrochloric, bovine serum albumin (BSA), 5, 5-dithiobis (2 nitrobenzoic acid) (DTNB), Folin–Ciocalteu's, hydrochloric acid, trichloroacetic acid and 2-thiobabituric acid (TBA) were purchased from Sigma–Aldrich (St. Louis, MO, USA). Vinpocetine and trihexylphenidyl hydrochloride (Himadri Specialty chemical Ltd, Bengal, India).

Laboratory animals: Adult Swiss male albino mice (15-21g) used in this study were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Nigeria. The animals were fed with rodent chow and had free access to drinking water. The experimental animals were generally maintained at 26±2°C and a relative humidity of about 55±5%.

Treatment regimen: Fifty-six mice were randomly divided into seven groups (n=8) and were orally treated as follows for 21 consecutive days; group I – vehicle, normal saline treated (normal control; 10ml/kg), group II – vinpocetine (20mg/kg), group III –vehicle (10ml/kg) + haloperidol (1mg/kg, i.p.), normal saline treated (PD model control; 10ml/kg), groups IV-VI - vinpocetine (5, 10 or 20 mg/kg, respectively) and group VII - trihexylphenidyl HCl (0.1mg/kg) for 21 consecutive days. Sixty minutes post-treatment animals in groups III-VII were given haloperidol (1mg/kg; i.p.) for 21 consecutive days.

Rotarod test: Mice were subjected to rotarod test to evaluate the effect of haloperidol and vinpocetine on muscle coordination. The apparatus consists of a horizontal metal rod (6 cm in diameter) attached to a motor with fixed speed. The rod is divided into five sections by a partition disc (10.5 cm in diameter). The rod was placed at a height of 50 cm to discourage the animals from jumping from the rotating rod. The animals were trained on the rotarod at a fixed speed of 20 rpm until they could remain on the apparatus for 300 s without falling 24 h before the experiments. Animals were subjected to rotarod test, one hour after drug or vehicle treatments on days 1, 4 and 11. The latency of falling within 5 min of test was recorded (Ishola *et al*., 2018).

Open Field test: To test effect of treatments on motor coordination and anxiety like behaviour, the open field test (OFT) was carried out. The apparatus was made of wood 50cm in length, 50cm in width and 25cm in height. The plain floor of the box was divided into 16 squares (8cm by 8cm). One-hour post oral administration, the mouse was gently placed at the centre of the open field apparatus and was allowed to acclimatize for 1 min, then the spontaneous activities were recorded for 5 mins. The following parameters were recorded: total number of crossing (number of times a mouse crosses from one square to another with all the four paws), total number of centre crossing (number of times a mouse enter the centre square where it was placed initially) (Ishola *et al*., 2014).

Y-maze test: The test relies on the innate tendency of mice to explore a novel environment to assess spatial recognition (Sarter *et al*., 1988). Animals were placed at the centre of the Y-maze facing the south arm 'B' and allowed to explore the maze freely for a period of 5 min. The number and the sequence of arm entries were observed. An arm entry was scored when all four paws were in the arm. Alternation behavior was defined as consecutive entries into all three arms (i.e., ABC, CAB, or BCA but not BAB). The percentage of spontaneous alternation was measured as an index of working memory by calculating the ratio of the actual number of alternations to the possible number (defined as the total number of arm entries minus two) multiplied by 100, i.e., % alternation [(number of alternations) / (total number of arm entries − 2)] − 100. The total number of arm entries was measured as an index of locomotor activity (Adedeji *et al*., 2014).

Catalepsy bar test (acute and chronic assays): Catalepsy bar test is widely used to measure the failure to correct an imposed posture resulting from muscular rigidity. It consists of placing a mouse forepaw on an elevated bar (4cm × 4cm) with the hind paws remaining on the floor. The time taken for the mouse to remove its paw from the bar, is an index of the intensity of catalepsy. A cataleptic mouse will continue to hold onto the bar for a prolonged period of time while a normal mouse will change its position within seconds (Adedeji *et al*., 2014) Hence, the ability of vinpocetine to ameliorate haloperidol-induced catalepsy was assessed using the bar test using the method of Adedeji *et al*. (2014). The bar is made up of wooden square bar (4cm × 4cm). Mice were gently positioned, placing their forelimbs on the bar and their hind limbs on the floor of the apparatus. The duration of catalepsy (animal is considered cataleptic if it maintained the imposed posture for at least 20 s), was recorded at 15, 30, 45, 90, and 120min for acute study on day 1. The endpoint of catalepsy was considered to occur when both forepaws were removed from the bar. A cut-off

time of 300 s was applied, all the observations were made in a quiet room. For the chronic study, catalepsy bar test was repeated on days 5, 9, 13, 17 and 21, respectively.

Brain perfusion and isolation: One hour after last treatment on day 21, mice were anaesthesized with chloral hydrate (300 mg/kg, i.p.) and perfused intracardially with chilled normal saline and brain was rapidly dissected out and rinsed in chilled phosphate buffer saline (0.03M) on ice. A 10% (w/v) homogenate of brain samples (0.03M sodium phosphate buffer, pH 7.4) was prepared by using an homogenizer at a speed of 9500 rpm. The homogenized tissue preparation was used to measure oxidative / nitrosative stress markers (Ishola *et al*., 2018).

Determination of oxidative/nitrosative stress markers: MDA an index of lipid peroxidation was determined using the method of Buege and Aust (1978), reduced glutathione (GSH), as non-protein sulphydryls was estimated according to the method described by Sedlak and Lindsay (1968). Catalase activity (CAT) was determined according to Sinha (1972). Superoxide Dismutase activity was determined by its ability to inhibit the auto-oxidation of epinephrine determined by the increase in absorbance at 480nm as described by Ishola *et al*. (2019). Nitrite was estimated in the brain using the Greiss reagent and served as an indicator of nitric oxide production (Green *et al*., 1982). Protein concentration was estimated using Lowry method (Upreti *et al*., 2012).

Statistical analysis

Values are expressed as mean ± SEM (n=8) and data analyzed using one- or two-way analysis of variance (ANOVA) followed by the Tukey's post-hoc multiple comparison tests. Level of statistical significance is $p<0.05$.

RESULTS

Rotarod performance test: Two way ANOVA revealed significant effect of treatments [F(6,105)=22.41,P<0.0001] and interaction between haloperidol and treatments [F(12,105)=3.67,P=0.0001]. Figure 1 showed that the intraperitoneal injection of haloperidol induced loss of muscle coordination on days 1, 4 and 11 when compared with vehicle treated control. However, co-administration of vinpocetine (5, 10 or 20 mg/kg) reversed haloperidol-induced motor deficit in mice.

Open Field Test: The administration of haloperidol reduced the number of crosses made by the mice when compared to the vehicle-control group (Table 1). However, vinpocetine (10mg/kg and 20mg/kg) treatment significantly ($p<0.01$) increased the number of crosses when compared to vehicle-treated haloperidol control on days 12, 15 and 18. Two way ANOVA showed significant effect of treatments (F(6,105)=17.21, $P<0.01$).

Y-maze test: The effect of vinpocetine on working memory was investigated in the spontaneous alternation behaviour Y-maze test. Haloperidol injection caused significant ($p<0.001$) decrease in relative proportion of spontaneous alternation behavior when compared to normal-vehicle treated control on days 6 and 9. However, the decrease in the relative proportion of spontaneous alternation behavior induced by haloperidol was reversed by vinpocetine (5, 10 and 20mg/kg) administration. Two way ANOVA revealed significant effect of treatments [F(6,105)=3.59,P<0.0001] and interaction between haloperidol and treatments [F(12,105)=2.68,P=0.0001] (Fig. 2).

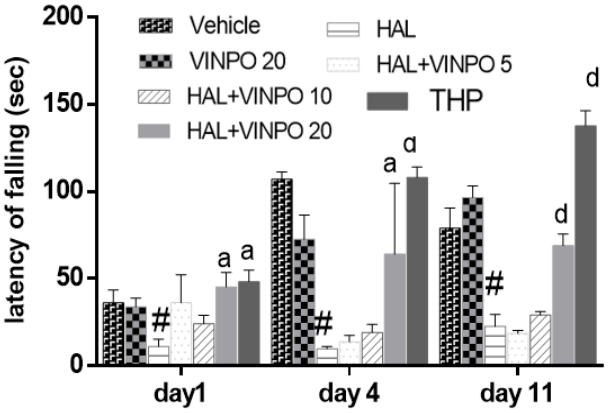

Figure 1:
Effect of vinpocetine on haloperidol-induced motor coordination on days 1, 4 and 10 in rotarod test. Values are expressed as mean±SEM (n=8). Significant levels of significance analysed by two-way ANOVA followed by Turkey post hoc multiple comparison tests. $^{\#}P<0.05$ versus vehicle 10ml/kg normal untreated mice; $^{a}P<0.05$, $^{d}P<0.0001$ versus HAL treated mice group. Key: VINPO = Vinpocetine, HAL = Haloperidol, THP = Trihexylphenidyl HCl.

Table 1:
Effect of haloperidol and vinpocetine on locomotor activity in open field test

Treatment	Dose (mg/kg)	day 12	day 15	day 18
vehicle	10ml/kg	67.40 ±2.06	61.80 ±2.59	62.00 ±6.76
vinpocetine	20	51.20 ±4.39	64.20 ±2.33	79.00 ±2.12
haloperidol	1	48.40 ±12.17$^{\#}$	25.80 ±4.11$^{\#}$	20.80 ±1.77$^{\#}$
vin+HAL	5+1	35.20 ±9.47	32.40 ±5.39	35.80 ±1.35
vin+HAL	10+1	62.40 ±12.87	53.60 ±3.66	54.00 ±2.00^{a}
vin+HAL	20+1	91.20 ±20.05^{b}	64.60 ±8.33^{b}	71.00 ±5.73^{d}
THP+HAL	0.1+1	64.40 ±4.13	75.60 ±1.24^{d}	71.00 ±1.87^{d}

Results are expressed as mean ± SEM (n = 8). $^{\#}P<0.05$ versus vehicle 10ml/kg normal untreated mice; $^{a}P<0.05$,$^{b}P<0.01$, $^{d}P<0.0001$ versus HAL-pretreated mice group. Statistical level of significance analysis by two way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. Key: VINPO = Vinpocetine, HAL = Haloperidol, THP = Trihexylphenidyl HCl.

Acute Haloperidol-induced catalepsy test: Oral administration of vinpocetine reversed the induced cataleptic effect of haloperidol in a dose dependent manner. Post hoc analysis showed that the intraperitoneal injection of haloperidol induced significant ($p<0.01$) cataleptic behaviour that peaked at 2 h post-treatment. In contrast, oral administration of vinpocetine produced significant and time

course reduction in haloperidol-induced cataleptic behaviour [F (6,105) =107.10, P< 0.0001] (Table 2).

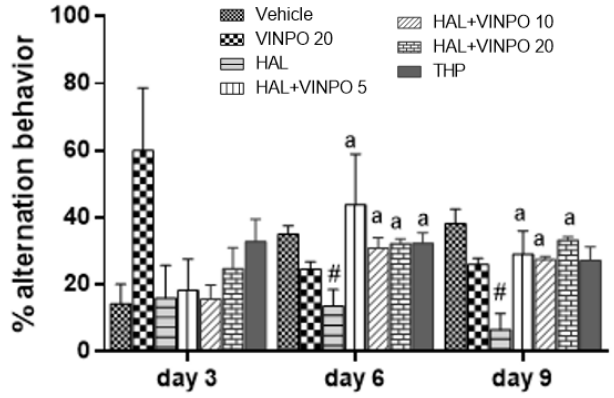

Figure 2:
Effect of vinpocetine treatment on haloperidol-induced working memory deficit in y-maze. Results are expressed as mean ± SEM (n = 8). $^{\#}P$<0.05 versus vehicle 10ml/kg normal untreated mice; ^{a}P<0.05 versus HAL-pretreated mice group. Statistical level of significance analysis by two way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. Key: VINPO = Vinpocetine, HAL = Haloperidol, THP = Trihexylphenidyl HCl.

Chronic haloperidol-induced catalepsy test: Chronic administration of haloperidol caused time course and significant (p<0.001) increase in cataleptic behaviour when compared with vehicle treated control mice. However, the pretreatment of mice with vinpocetine (5, 10 and 20 mg/kg) or triheylphenidyl before haloperidol injection over a period of 21 days significantly reduced the cataleptic behaviour when compared with vehicle-haloperidol treated group (Table 3).

Biochemical evaluation

MDA Measurement: Administration of haloperidol for 2 consecutive days caused significant (p<0.001) increase lipid peroxidation (2 folds) F (6, 28) = 3.963;p<0.005 (Fig. 4a), deficits in GSH level (F(6, 28)=10.37;p<0.001) (Fig. 4b), catalase activities F (6, 28) = 6.127,p<0.001) (Fig. 4c), superoxide dismutase activities F (6, 28) = 17.11,p<0.001) (Fig. 4d) and increase in nitrite generation F (6, 28) = 5.23,p<0.01) (Fig. 4e) in the brain. Haloperidol-induced MDA and nitrite generation were attenuated by vinpocetine administration. Similarly, haloperidol induced decrease in GSH level , catalase and SOD activities were enhanced by vinpocetine administration.

Table 2:
Time course effect of vinpocetine on haloperidol-induced catalepsy in mice

Treatment	Dose (mg/kg)	15mins	30 mins	60 mins	90 mins	120 mins
vehicle	10ml/kg	1.17 ± 0.83	1.17 ± 0.28	0.54 ± 0.24	0.51 ± 0.23	0.33 ± 0.33
VINPO	20	6.33 ± 2.01	1.20 ± 0.16	0.63 ± 0.20	0.50 ± 0.22	0
HAL	1	39.17 ± 13.02$^{\#}$	30.33 ± 8.91$^{\#}$	22.67 ± 4.67$^{\#}$	74.50 ± 3.57$^{\#}$	80.83±13.81$^{\#}$
vin+HAL	5+1	8.17 ± 2.64^{d}	16.17 ± 2.38	7.50 ± 0.67	3.17 ± 0.30^{d}	4.17±0.30^{d}
vin+HAL	10+1	5.83 ± 3.54^{d}	8.16 ± 1.42^{b}	2.09 ± 0.85^{a}	2.58 ± 1.05^{d}	4.50±0.42^{d}
vin+HAL	20+1	2.00 ± 0.25^{d}	4.00 ± 0.36^{d}	2.33 ± 0.21^{b}	1.31 ± 0.15^{d}	0.49±0.13^{d}
THP+HAL	0.1+1	1.58 ± 0.07^{d}	5.5 ± 0.85^{c}	4.67 ± 0.55^{a}	4.50 ± 0.43^{d}	2.83±0.30^{d}

Values are expressed as mean±SEM (n=8). Results are expressed as mean±SEM (n = 8). $^{\#}P$<0.05 versus vehicle 10ml/kg normal untreated mice; ^{a}P<0.05; ^{b}P<0.01; ^{d}P<0.0001 versus HAL-pretreated mice group. Statistical level of significance analysis by two way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. Key: VINPO = Vinpocetine, HAL = Haloperidol, THP = Trihexylphenidyl HCl.

Table 3:
Effect of vinpocetine on chronic haloperidol-induced catalepsy in mice

Treatment	Dose (mg/kg	Catalepsy scores (sec)				
		Day 5	Day 9	Day 13	Day 17	Day 21
Vehicle	10ml/kg	1.33±0.16	1.50±0.34	2.33±0.21	2.33±0.21	2.83±0.30
Vinpo	20	6.83±2.45	6.00±1.67	7.83±1.30	15.67±1.52	15.17±0.60
HAL	1	30.18±10.46$^{\#}$	29.00±5.87$^{\#}$	50.50±8.24$^{\#}$	115.00±0.77$^{\#}$	149.17±8.40$^{\#}$
Vinpo+HAL	5+1	13.32±4.87^{b}	9.17±2.96^{c}	12.35±3.51^{d}	16.17±1.90^{d}	38.00±0.73^{d}
Vinpo+HAL	10+1	5.50±1.56^{d}	7.30±1.84^{c}	7.30±0.42^{d}	10.17±0.91^{d}	12.67±0.42^{d}
Vinpo+HAL	20+1	4.85±3.24^{d}	6.75±1.89^{d}	3.50±0.42^{d}	5.16±0.54^{d}	5.83±0.79^{d}
THP+HAL	0.1+1	3.88±2.42^{d}	8.16±1.13^{c}	0.71±0.36^{d}	16.50±1.05^{d}	19.00±0.57^{d}

Results are expressed as mean±SEM (n=8). The results were analyzed by two-way ANOVA followed by Tukey post hoc tests. Significant reduction in the duration of catalepsy [$^{\#}P$<0.0001 versus vehicle-treated group; ^{b}P<0.01, ^{c}P<0.001, ^{d}P<0.0001 versus HAL (1mg/kg, i.p.) treated group}.

DISCUSSION

The present study investigated the effect of vinpocetine on haloperidol induced cognitive and motor impairments in mice. In this study, subchronic administration of haloperidol caused time course increase in catalepsy and motor deficit which is in agreement with our previous study (Adedeji *et al*., 2014). However, haloperidol-induced catalepsy in bar test, motor deficit in open field test and cognitive impairment in Y-maze task were ameliorated by vinpocetine administration. In addition, haloperidol-induced increase in oxidative and nitrosative radicals' generation as well as deficit in antioxidant enzymes activities were reversed by vinpocetine administration.

Several studies have revealed novel actions of vinpocetine, including anti-inflammation, antagonizing injury-induced vascular remodeling and high-fat-diet-induced atherosclerosis, as well as attenuation pathological cardiac remodeling (Cai *et al*., 2012; Zhang *et al*., 2018).

Cai *et al*. (2012) showed that systemic administration of vinpocetine significantly reduced neointimal formation, spontaneous remodeling, dose-dependently suppressed cell proliferation and caused G1-phase cell cycle arrest, which is associated with a decrease in cyclin D1 and an increase in p27Kip1 levels. Thus, repositioning of vinpocetine for preventing or treating neurodegenerative disorders in humans (Zhang *et al*., 2018). In this study, vinpocetine prevents catalepsy, motor-imbalance (rotarod) and cognitive deficits as well as oxidative stress induced by haloperidol.

Haloperidol produced Parkinson-like syndromes and extrapyramidal symptoms in psychiatric patients (Mohajjel-Nayebi and Sheidaei, 2010). The phenomenon of cataleptic immobility induced in mice by the use of dopamine antagonist such as haloperidol is widely used to assess nigrostriatal function in rodents (Barroca *et al*., 2019). In this study subchronic administration of haloperidol-induced cataleptic behaviour suggestive of reduced nigriostriatal signaling which was ameliorated by vinpocetine. Moreover, reduction of muscle coordination in rotarod test indicates possible neurotoxic effect of haloperidol (Kumari *et al*., 2018), which was ameliorated by vinpocetine administration. Moreover, vinpocetine prevented haloperidol-induced spatial working memory impairment in the Y-maze test.

Oxidative stress to dopaminergic neurons of substantia nigra pars compact is believed to be one of the leading causes of neurodegeneration in PD. It has been suggested that reactive oxygen species (ROS) play a role in the neuronal damage occurring in ischemic injury and neurodegenerative disorders and that their neutralization by antioxidant drugs may delay or minimize neurodegeneration (Santos *et al*., 2000). Interestingly, chronic administration of haloperidol increased MDA, nitric oxide and decreased GSH in selected brain regions (Pereira *et al*., 2003; Adedeji *et al*., 2014). Findings from this study revealed that vinpocetine mitigated haloperidol increased malondialdehyde and nitrite generation as well as reduction of GSH, catalase and SOD activities in the brain. Interestingly, in vitro studies have reported the protective effect of vinpocetine against ROS attacks (Santos *et al*., 2000; Pereira *et al*., 2003).

In conclusion, findings from this study suggests that vinpocetine prevented haloperidol-induced cognitive and motor impairments through attenuation of oxidative and nitrosative stress. Thus, vinpocetine could be a potential adjunct in the management of Parkinson disease.

Acknowledgement

Authors are grateful to Mr. M. Chijioke of the Department of Pharmacology, Therapeutics and Toxicology, College of Medicine University of Lagos for his technical assistance

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