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ORIGINAL ARTICLE

Vinpocetine regulates levels of circulating TLRs in Parkinson's disease patients

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Abstract

Background The pathogenesis of Parkinson's disease (PD) is complex; it includes mitochondrial dysfunction, oxidative stress, and neuroinflammation. Notably, Toll-like receptors (TLRs) may activate inflammatory or anti-inflammatory responses in Parkinson's disease. Vinpocetine has been tested as an anti-inflammatory in both animal and in vitro research. Thus, it is important to test whether the anti-inflammatory properties of vinpocetine may have a protective effect in PD patients.

Methods Eighty-nine Parkinson's disease patients and 42 healthy controls were recruited for this study. All patients were randomly assigned to either the traditional therapy group (T PD group, $n = 46$) or the vinpocetine group (V PD group, $n = 43$), in a blinded manner. Both treatments were administered for 14 days.

Results Administration of vinpocetine reduced mRNA levels of *TLR2/4*, as well as protein levels of the downstream signalling molecules, MyD88 and NF-κB; moreover, it lowered the expression levels of serum inflammatory cytokines, TNF-α and MCP-1. Notably, vinpocetine increased *TLR3* mRNA levels, as well as protein levels of the downstream signalling molecules TRIF-β and IRF-3, and serum levels of the anti-inflammatory cytokines IL-10 and IL-8. Furthermore, vinpocetine produced a robust increase in the Mini Mental State Examination score, compared to that achieved by using levodopa therapy.

Conclusion Vinpocetine treatment may exhibit anti-inflammatory activity and alleviate cognitive impairment.

Keywords Parkinson's disease · TLRs · Vinpocetine · Neuroinflammation

Introduction

Parkinson's disease (PD) is a well-characterised neurodegenerative disorder that is imposing a growing burden on the global ageing population. Although the pathogenesis of PD is complex, several hallmarks of this disease have been well-characterised, namely mitochondrial dysfunction, oxidative stress, and neuroinflammation [1–3]. Moreover, several PD animal models have suggested that specific inflammatory signals may be responsible for dopaminergic cell loss.

Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system; notably, TLRs bind to pathogen-associated molecular patterns and damage-associated molecular patterns. TLR activation induces the release of anti-inflammatory or pro-inflammatory molecules, depending on the activation of specific pathways. Increasing evidence suggests that TLRs may play an important role in neurodegenerative disorders [4]. Recent studies have shown that blocking TLR2 can reduce nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and secretion of tumour necrosis factor alpha (TNF-α) from cultured primary mouse microglia; further, TLR4-mediated cell death in a mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [5, 6]. Furthermore, TLR2 and TLR4 polymorphisms have been associated with sporadic PD [7, 8]. However, priming a lesion-induced PD model with the TLR3 dsRNA inflammatory stimulant Poly (I:C) has been reported to provide a

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significant neuroprotective effect [9]. Therefore, TLRs provide promising candidates for the development of PD therapies.

Vinpocetine is a semisynthetic derivative of the vinca alkaloid vincamine; it is used as both a neuroprotective and cerebral-blood-flow-enhancing agent [10, 11]. Vinpocetine is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory and cerebral metabolism. In vitro tests have shown that vinpocetine prevents upregulation of LPS-induced NF-κB activation and cytokine production (TNF-α, IL-1β, and IL-33) through a phosphodiesterase-dependent pathway in vascular smooth cells, human umbilical vein endothelial cells, a macrophage cell line, and lung epithelial A549 cells [12–14].

The present study was undertaken to assess the effect of vinpocetine administration on levels of TLRs and to determine whether vinpocetine exhibits a protective effect in PD patients.

Population and methods

Subjects

This double-blinded, case-control study was approved by the institutional ethics committees of Wenzhou Medical University and conforms to the principles of the Declaration of Helsinki. Informed consent was obtained from all subjects. All recruited subjects had been diagnosed with late-onset Parkinson's disease at the Second Affiliated Hospital of Wenzhou Medical University.

Forty-two healthy controls and 89 PD patients were recruited. All 89 patients were randomly assigned to either the traditional therapy group (T PD group, $n = 46$) or the vinpocetine group (V PD group, $n = 43$). In both traditional therapy and vinpocetine groups, levodopa (250 mg bid) was applied from the first day to the target day (14th day), in accordance with the guideline of Parkinson's disease diagnosis and treatment. Vinpocetine (20 mg) in saline solution (250 ml, 0.9%) was administered daily to patients in the V PD group. Saline solution (250 ml, 0.9%) was administered to the healthy control subjects and patients in the traditional therapy group. No pharmacological treatment was administered to the healthy control subjects. The PD patients discontinued any other medications, aside from levodopa, for the duration of the study.

Patients were excluded from the present study if they had a history of any of the following conditions: acute decompensated heart failure, ischaemic heart disease, serious arrhythmias, haemorrhage, shock, advanced liver disease, or autoimmune diseases.

Sample size

The sample size was estimated using the following formula, as previously described [15]:

$$N = Z^2 \times (P \times (1-P))/E^2$$

where N = sample size; Z = statistics size; P = probability value; E = error. CI (confidence interval) = 95%. The minimum sample size necessary to achieve statistical power was estimated at 30 per group.

mRNA expression detection

mRNA was sampled from subjects (peripheral blood monocytes were collected by centrifugation of patient blood samples for 20 min at 3000× g) at the beginning of therapy (day 1) and 14 days after the completion of therapy. *TLR2*, *TLR3*, and *TLR4* mRNA expression levels were analysed by using a two-step method of quantitative real-time reverse transcription polymerase chain reaction (RT-PCR). SYBR Premix EX Taq (TAKARA, Japan), 200 ng of cDNA template, and a set of TLR primers were mixed as a reaction mixture for reverse primer. The sequences of the *TLR2* forward and reverse primers were 5′-CAA TGA TGC TGC CAT TCT CAT-3′ and 5′-ATT ATC TTC CGC AGC TTG CA-3′, respectively. The sequences of the *TLR3* forward and reverse primers were 5′-ATT AGG AAC TCA GGT TCA GC-3′ and 5′-GGA CAT TGT TCA GAA AGA GG-3′, respectively. The sequences of the *TLR4* forward and reverse primers were 5′-TGC GGG TTC TAC ATC AAA-3′ and 5′-CCA TCC GAA ATT ATA AGA AA AGT C-3′, respectively. *GAPDH* mRNA was used to correct the mRNA loading quantities. PCR was performed by using IQ5 Multicolor Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA). The $2^{-\Delta\Delta CT}$ method was used to calculate the data.

Western blot

Proteins were obtained from peripheral blood monocytes at the beginning of therapy (day 1) and 14 days after the completion of therapy. Briefly, 20 μg of proteins were separated by SDS-precast gel and transferred to polyvinylidene fluoride membranes. After blocking, the filters were incubated with the following antibodies at 4 °C overnight: anti-human TIR domain-containing protein-β antibody (1:1200; TRIF-β, ab13810, Abcam, USA), anti-human myeloid differentiation factor 88 antibody (1:1000; MyD88, bs3521, Bioworld, USA), anti-nuclear factor-kappa B antibody (1:1200; NF-κB p65, ab16502, Abcam, USA), and anti-human interferon regulatory factor 3 antibody (1:1200; IRF3, ab21680, Abcam, USA). After washing and a 2-h incubation with the corresponding secondary antibody (alpha tubulin for TFIR-β and

MyD88; GAPDH for NF-κB and IRF-3, Amersham), the membranes were visualised by a chemiluminescence method (ECL Western blotting detection system).

Serum inflammatory factor detection

At the beginning of therapy (day 1) and 14 days after the completion of therapy, serum levels of TLR2, TLR3, TLR4, TNF-α, monocyte chemoattractant protein 1 (MCP-1), interleukin-10 (IL-10), and interleukin-8 (IL-8) were measured in accordance with manufacturers' instructions (TLR2 ELISA kit, SEA663Hu, USCN Business Co., Ltd., Wuhan, China; TLR3 ELISA kit, ABIN417426, antibodies-online; TLR4 ELISA kit, ABIN414556, antibodies-online; Human MCP-1 TNF-alpha; IL-8 and IL-10 Quantikine ELISA kit, R&D Systems).

Parkinson's disease rating scale

Both on the first day of therapy and 14 days after the completion of therapy, the following rating scales were used to assess movement, emotion, and cognitive function conditions in all groups: The Unified Parkinson's Disease Rating Scale-Iii (UPDRS-III), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Mini-Mental State Examination (MMSE).

In SDS and SAS data collection, patients' self-evaluations were scored from 1 to 4, as 1—never; 2—rarely; 3—sometimes; and 4—almost always. High scores in UPDRS-III, SAS, and SDS indicated the presence of severe PD symptoms, while low scores in MMSE were associated with low cognitive function.

Statistical analysis

All analyses were performed by using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data are represented as mean ± SEM, or median and interquartile range for *t* test and one-way ANOVA analyses. A p value less than 0.05 was considered statistically significant. All p values were corrected for multiple comparisons; all experiments were performed at least three times.

Results

Subjects' clinical data

The clinical characteristics of the three groups are shown in Table 1. No significant differences were found among the three groups with respect to age, gender, smoking, drinking, diabetes, body mass index, waist to hip ratio, white blood cell count, or high-sensitivity C-reactive protein levels.

Vinpocetine changes TLRs mRNA expression levels

In Fig. 1, real time-PCR was used to detect mRNA expression of TLRs in healthy controls and in PD patients, both before and after treatment. *TLR2* and *TLR4* mRNA expression levels in healthy subjects were significantly lower than those

Table 1 The subjects' characters

	Healthy control ($n = 42$)	Parkinson's disease patients		P value in three group
		T PD group($n = 46$)	V PD group($n = 43$)	
Age	60 ± 3	61 ± 4	59 ± 3	0.828
Gender(M/F)	21:21	23:23	21:22	0.921
Smoking	10 (23%)	12 (26%)	11 (25%)	0.756
Drinking	22 (52%)	23 (50%)	21 (48%)	0.629
Diabetes	10 (23%)	11 (24%)	10 (23%)	0.952
BMI (kg/m)	24.11 ± 1.02	24.75 ± 1.77	23.67 ± 1.52	0.813
WHR	1.013 ± 0.071	1.245 ± 0.085	1.177 ± 0.101	0.781
WBC ($\times 10^9$/l)	6.45 ± 1.33	7.12 ± 1.45	5.76 ± 1.11	0.845
hs-CRP(mg/l)	1.87 (1.56, 2.04)	2.17 (1.48, 2.34)	1.96 (1.63, 2.15)	0.652
Medication history				
Levodopa	0	46	43	1
Vinpocetine	0	0	43	1

Data are represented as mean ± SEM, or median and interquartile range (hs-CRP)

BMI, body mass index; *WHR*, waist-to-hip ratio; *WBC*, white blood cell; *hs-CRP*, high-sensitivity C-reactive protein. $P < 0.05$ was considered statistically significant in three groups. $n = 42$ in healthy control, $n = 89$ in Parkinson's disease baseline group, $n = 46$ in traditional therapy group, and $n = 43$ in vinpocetine group

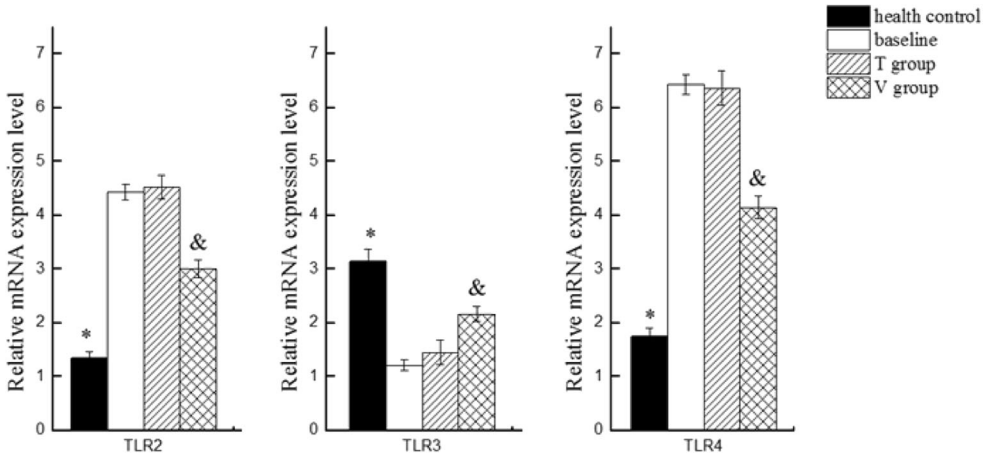

Fig. 1 Real time-PCR was applied to detect TLR mRNA expression. mRNA levels of *TLR2*, *TLR3*, and *TLR4* were detected on the first day of therapy and 14th day after therapy in Parkinson's disease patients. $^{*}P < 0.05$, healthy control was compared with baseline of Parkinson's disease patients, T PD group, and V PD group. $^{\&}P < 0.05$, V PD group was compared with healthy group, baseline of Parkinson's disease patients, and T PD group. $n = 42$ in healthy control, $n = 89$ in Parkinson's disease baseline group, $n = 46$ in traditional therapy group, and $n = 43$ in vinpocetine group

measured at baseline in PD patients, both T PD and V PD groups (TLR2, $p = 0.021$; TLR4, $p = 0.027$). However, *TLR3* levels in healthy controls were noticeably higher than those measured at baseline in PD patients, both T PD and V PD groups ($p = 0.033$). Fourteen days after the completion of the treatment, vinpocetine, compared with levodopa treatment, promoted a robust reduction of *TLR2* and *TLR4* mRNA expression. In contrast, *TLR3* mRNA expression in PD patients ($p = 0.026$) was significantly higher in the V PD group, compared with the T PD group.

Vinpocetine regulates TLRs downstream signalling proteins

As shown in Fig. 2, TRIF-β and IRF3 were primarily regulated by TLR3. In contrast, MyD88 and NF-κB were

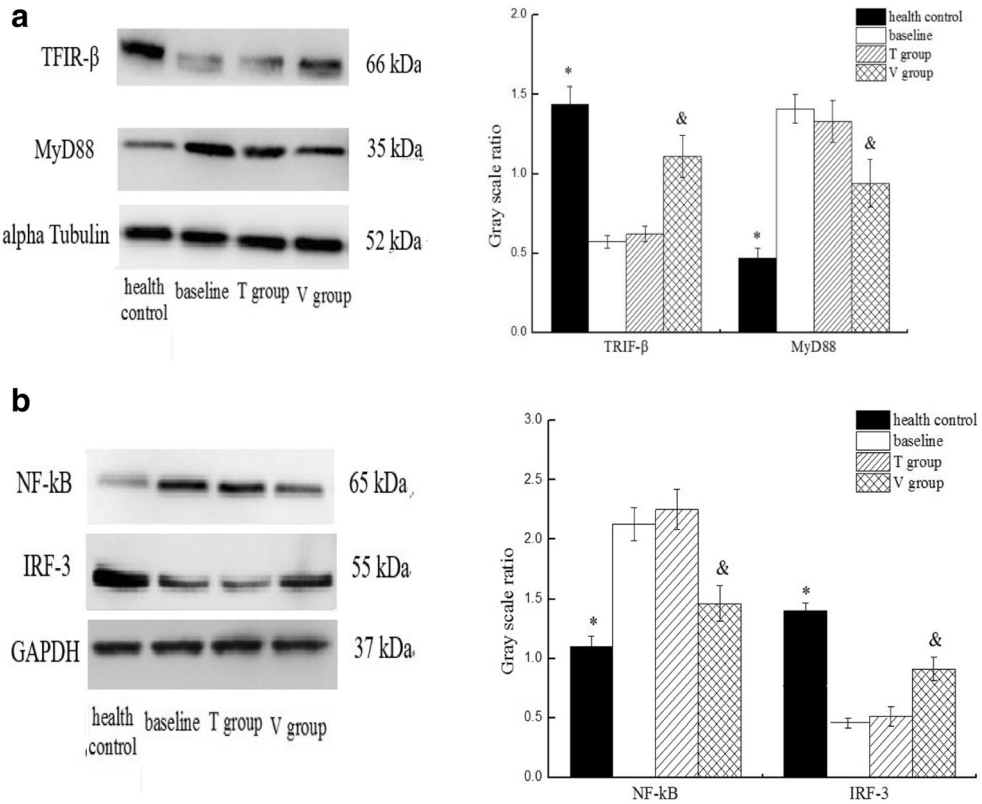

Fig. 2 TLR downstream signalling proteins were detected by Western blotting. TRIF-β, TIR domain-containing protein-β; MyD88, myeloid differentiation factor 88; NF-kB, nuclear factor-kappa B; IRF3, interferon regulatory factor 3. $^{*}P < 0.05$, healthy control was compared with baseline of Parkinson's disease patients, T PD group, and V PD group. $^{\&}P < 0.05$, V PD group was compared with healthy group, baseline of Parkinson's disease patients, and T PD group. $n = 42$ in healthy control, $n = 89$ in Parkinson's disease baseline group, $n = 46$ in traditional therapy group, and $n = 43$ in vinpocetine group

affected by TLR2/4. In the healthy control group, TRIF-β and IRF3 protein levels were higher than those measured at baseline in PD patients, both T PD and V PD groups ($p = 0.034$). However, MyD88 and NF-κB protein levels were significantly lower in the health control group, compared with those measured at baseline in PD patients, both T PD and V PD groups ($p = 0.019$). Levodopa treatment had less influence on baseline expression of TRIF-β, MyD88, NF-kB, and IRF3 in PD patients, both T PD and V PD groups ($p > 0.05$). Vinpocetine treatment promoted upregulation of TRIF-β and IRF3, compared with all PD patients at baseline and the T PD group ($p = 0.030$). In addition, vinpocetine induced downregulation of MyD88 and NF-κB, compared with all PD patients at baseline and the T PD group ($p = 0.029$).

Vinpocetine regulates serum inflammatory factors

Measurements of TLRs and other associated inflammatory factors are reported in Table 2. TLR2, TLR4, MCP-1, and TNF-α were significantly lower in the control group, compared with T PD and V PD groups at baseline ($p = 0.031$, for all comparisons). However, TLR3, IL-10, and IL-8 were significantly higher in the control group, compared with T PD and V PD groups at baseline ($p = 0.034$, for all comparisons). Following levodopa administration, levels of all inflammatory factors exhibited minimal changes, compared with all PD patients at baseline ($P > 0.05$). Notably, vinpocetine administration significantly reduced serum levels of TNF-α, MCP-1, TLR2, and TLR4 at 14 days after the completion of the treatment, relative to the baseline levels of all PD patients. In contrast, IL-8, IL-10, and TLR3 levels after the treatment were notably higher in the V PD group, compared with the levels measured in the T PD group ($p = 0.028$).

Parkinson's disease rating scale

Table 3 shows the results of assessments with the following scales: the UPDRS-III scale, used to assess movement in PD patients; the SAS and SDS scales, used to assess emotion; and the MMSE, used to evaluate cognitive function. PD patients had a significantly higher rating than the control group in PD movement and emotion assessments. However, PD patients scored lower in cognitive function ($p = 0.022$). After 14 days of treatment, the V PD and T PD groups exhibited an improvement in cognitive performance, as demonstrated by an increase in MMSE scores (Table 3); the V PD group demonstrated a greater improvement in cognitive function ($p = 0.025$). However, these follow-up scores were lower than those of healthy controls ($p = 0.031$). Furthermore, vinpocetine appeared to positively affect PD cognitive function ($p = 0.021$).

Discussion

The present study showed that vinpocetine reduces TLR2/3/4-circulating levels in PD patients and improves cognitive function scores. However, this study did not determine whether a causal link exists between TLR2/3/4 expression and cognitive function scores in PD patients.

There is a strong association involving PD, inflammatory responses, and immune abnormalities [16]. Inflammatory factors induce neurons, microglia, and astrocyte death, which all may contribute to deleterious effect of neuroinflammation and protective effect of immunity in neurodegenerative disease. Microglia play a protective role by removing apoptotic cells and protein aggregates [4] and play a detrimental role by expressing various TRLs and stimulating the production of pro-inflammatory cytokines such as TNF-α and IL-6 and chemokine such as CXCL8 [17]. Indeed, a polymorphism in the

Table 2 Serum inflammatory

	Control ($n = 42$)	Baseline ($n = 89$)		Treatment ($n = 89$)	
		T PD group ($n = 46$)	V PD group ($n = 43$)	T PD group ($n = 46$)	V PD group ($n = 43$)
TLR2 (pg/ml)	261.32 ± 15.71*	408.35 ± 26.11	411.26 ± 25.42	425.41 ± 21.67	316.76 ± 23.56$^{\&}$
TLR3 (pg/ml)	328.33 ± 24.61*	192.35 ± 17.46	196.21 ± 16.83	201.33 ± 17.46	261.15 ± 22.53$^{\&}$
TLR4 (pg/ml)	217.56 ± 11.13*	468.97 ± 30.15	470.26 ± 32.11	456.73 ± 29.33	337.52 ± 28.41$^{\&}$
TNF-α (pg/ml)	22.43 ± 2.32*	42.14 ± 4.03	42.63 ± 3.79	41.17 ± 4.19	31.56 ± 4.25$^{\&}$
MCP-1 (pg/ml)	623.22 ± 39.74*	801.66 ± 58.69	789.74 ± 58.42	864.71 ± 61.14	742.71 ± 61.71$^{\&}$
IL-10 (pg/ml)	22.01 ± 2.79*	13.67 ± 1.31	13.15 ± 1.52	12.82 ± 1.77	18.03 ± 1.82$^{\&}$
IL-8 (pg/ml)	27.72 ± 7.10*	15.41 ± 1.28	15.51 ± 1.38	16.34 ± 1.43	20.93 ± 2.03$^{\&}$

TLR, Toll-like receptor; *TNF-a*, tumour necrosis factor-a; *MCP-1*, monocyte chemotactic protein 1; *IL*, interleukin. *$P < 0.05$, healthy control was compared with baseline of Parkinson's disease patients, T PD group, and V PD group. $^{\&}$ $P < 0.05$, V PD group was compared with healthy group, baseline of Parkinson's disease patients, and T PD group

Table 3 Parkinson's disease rating scale

	Control ($n = 42$)	Baseline ($n = 89$)		Treatment ($n = 89$)	
		T PD group ($n = 46$)	V PD group ($n = 43$)	T PD group ($n = 46$)	V PD group ($n = 43$)
UPDRS-III	3.21 ± 0.65*	19.05 ± 2.42	19.58 ± 2.46	15.32 ± 3.93^	16.11 ± 4.09^
SAS	36.12 ± 3.09*	65.04 ± 4.37	64.67 ± 4.51	55.73 ± 4.09^	57.73 ± 5.31^
SDS	38.69 ± 3.77*	72.16 ± 8.11	72.09 ± 8.52	52.72 ± 6.87^	52.72 ± 6.87^
MMSE	26.53 ± 2.82*	16.17 ± 2.14	16.79 ± 2.93	18.72 ± 1.91^	22.11 ± 2.77^&

UPDRS-III, the Unified Parkinson's Disease Rating Scale-III; *SAS*, Self-Rating Anxiety Scale; *SDS*, Self-Rating Depression Scale; *MMSE*, Mini-Mental State Examination. *$P < 0.05$, healthy control was compared with baseline of Parkinson's disease patients, T PD group, and V PD group. & $P < 0.05$, V PD group was compared with healthy group, baseline of Parkinson's disease patients, and T PD group. ^$P < 0.05$, T PD group was compared with baseline of Parkinson's disease patients

TNF-α gene has been shown to correlate with early onset of sporadic PD in the Japanese population [18, 19]. TLR2/4 induced pro-inflammatory signalling in astrocytes and microglia upon treatment of a mouse model of PD with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Interference with TLRs that promote or degrade inflammation may regulate downstream signalling pathway transcription of cytokines (e.g. TNF-α, MCP-1, and IL) leading to an overall imbalance of oxidative stress in dopamine neurons [6, 20].

TLRs have significant roles in innate and adaptive immunity. On the basis of variations in subcellular localization and PAMP ligands with which they interact, there are two subgroups of TLRs: plasma membrane and intracellular endosome [21] The primary ligand for TLR1 is a bacterial triacy1-lipopeptide; TLR 1 is located in myeloid cells, T cells, B cells, NK cells, microglia, and astrocytes. TLR5 recognises flagellin. TLR7, TLR8, and TLR9 are homologous and can identify microbial nucleic acids by combining their ligands in the endosome; they bind to a bacterial CpG-DNA, which activates the immune-stimulating properties of B cells and APC [22]. Notably, TLR2, TLR3, and TLR4 are associated with serum lipid metabolic disturbances, atheromatous plaque formation, risk of diabetes mellitus, and ischemia injury, in addition to their specific relationship with PD [22–24].

Recent reports have provided evidence that TLRs and their ligands play a crucial role in neuronal cell injury and death in PD. Fellner and colleagues have shown that TLR4 mediates alpha-synuclein-induced microglial phagocytic activity, pro-inflammatory cytokine release, and production of reactive oxygen species. [23] In 6-OHDA and rotenone models, TLR4 and the viral-responsive TLR3 are present in the inflamed striatum; TLR4 and TLR2 activation is differentially associated with age during PD [24].

Vinpocetine is a nootropic drug widely used to treat cognitive and neurovascular disorders. Recently, its therapeutic properties have been described in the context of the inhibition of NF-κB activation and NF-κB-related cytokine production in macrophages. In addition, in vitro experiments have shown that vinpocetine reduces TNF-α-induced expression of NF-κB, IL-1β, and MCP-1 [25]. In our study, vinpocetine significantly reduced levels of proteins in the TLR2/4-MyD88-NF-κB signalling pathway, as well as inflammatory cytokines, TNF-α and MCP-1. Moreover, it increased levels of proteins in the TLR3-TRIF-β-IRF3 signalling pathway, as well as anti-inflammatory cytokines, IL-10 and IL-8. Some research has shown that TLR2 and TLR4 expression is increased in PD brains, according to disease stage, and correlated with α-synuclein pathology. Inhibition of TLR2/4-MyD88-NF-κB signalling pathways can attenuate α-synuclein-mediated neurodegeneration; this is achieved by either knockout or knockdown of TLR2 in rodent PD models. Importantly, this is relevant to the present study because vinpocetine reduced TLR2 mRNA, as well as its protein expression; thus, it may be an effective therapeutic intervention [26, 27].

Furthermore, vinpocetine has been shown to facilitate potentiation, improve spatial memory, and enhance cognition via direct inhibition of phosphodiesterase, eventually leading to enhancements in cAMP and cGMP levels [28–30]. In the present study, vinpocetine administration was associated with a high MMSE score in PD patients, suggesting that both memory processes and cognition were improved in these patients. However, it is not clear whether the anti-inflammatory properties of vinpocetine have a protective effect in PD patients. Some authors have suggested that its neuroprotective effects are achieved through enhancement in cerebral blood flow [31, 32]. This might explain why the benefits of vinpocetine are limited to cognitive impairment in PD, rather than other non-motor and motor symptoms. To our knowledge, few studies have investigated the mechanism underlying the beneficial effects of vinpocetine on PD symptoms. A variety of studies (clinical and experimental) has proposed that vinpocetine may achieve its neuroprotective effects through several concurrent mechanisms. Nonetheless, because no significant adverse effects of vinpocetine administration have been

reported either in our study, in the literature, or in clinical practice, it is generally considered safe for short-term use.

It is also not clear whether the difference in scores from 18.72 to 22.11 albeit statistically significant is clinically significant especially as the controls also improved from 16.05 to 18.72, so that there may be a learning effect. A change of two points is well within the standard deviation of repeated testing [33]. The overall cohort was impaired, with low baseline MMSE scores that are typically indicative of advanced PD. However, it is necessary to perform an investigation including a longer follow-up and a larger patients' sample to confirm the vinpocetine protective effect on cognitive deterioration in Parkinson's disease. Furthermore, levodopa is a classical medication in PD therapy, which improves movement dysfunction, but does not affect inflammation or cognitive dysfunction. [34, 35]

In summary, the present study has uncovered an anti-inflammatory role for vinpocetine in the treatment of PD. Vinpocetine regulates TLR2/3/4 mRNA and protein expression; moreover, it modulates downstream signalling proteins and cytokines. However, there is no stable or clear cause-effect relationship between its anti-inflammatory action and cognitive enhancement. Thus, vinpocetine is a good candidate for future therapy in PD patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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