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Pharmacological study on the potential effects of Filgrastim in rotenone-induced model of Parkinson's disease in rats

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Contents

List of Abbreviations

Ab	Antibody
AD	Alzheimer's disease
AKT	Protein kinase B
ALS	Amyotrophic lateral sclerosis
ALSFRS	ALS functional rating scale
ANOVA	Analysis of variance
APAF1	Apoptotic protease-activating factor 1
Bad	Bcl-2-associated death promoter
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CBD	Corticobasal degeneration
CNS	Central nervous system
COMT	Catechol-*O*-methyl transferase
CPR	Crude prevalence rate
CSF	Cerebrospinal fluid
DA	Dopamine
DAT	Dopamine transporter
DMSO	Dimethyl sulfoxide
EAE	Experimental autoimmune encephalomyelitis
ECD	Electrochemical detector
EDTA	Ethylenediaminetetraacetic acid
ERK	Extracellular signal-regulated kinase
^{18}F-DOPA	^{18}F-fluorodopa
G-CSF	Granulocyte colony-stimulating factor
G-CSFR	Granulocyte colony-stimulating factor receptor
GPe	Globus pallidus external segment
GPi	Globus pallidus internal segment
GSK-3β	Glycogen synthase kinase-3β
GWAS	Genome-wide association studies
H&E	Hematoxylin and eosin

HPLC	High-performance liquid chromatography
HRP	Horseradish peroxidase
i.p.	Intraperitoneal
i.v.	Intravenous
Iba-1	Ionized calcium-binding adapter molecule-1
IL-1β	Interleukin-1β
IQR	Interquartile range
IR	Infrared
JAK2	Janus kinase 2
LB	Lewy body
L-DOPA	Levodopa
LRRK2	Leucine-rich repeat kinase 2
MAO	Monoamine oxidase
MAP kinase	Mitogen-activated protein kinase
MPP^+	1-Methyl-4-phenylpyridinium
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NF-κB	Nuclear factor-kappa B
NMDA	*N*-methyl-*D*-aspartate
OD	Optical density
6-OHDA	6-Hydroxydopamine
PBS	Phosphate-buffered saline
PD	Parkinson's disease
PET	Positron emission tomography
PI3K	Phosphatidylinositol 3-kinase
*p*NA	*p*-Nitroaniline
PSP	Progressive supranuclear palsy
RBD	Rapid eye movement sleep behavior disorder
ROS	Reactive oxygen species
s.c.	Subcutaneous
SEM	Standard error of mean
SNc	*Substantia nigra pars compacta*

SOD	Superoxide dismutase
SPECT	Single photon emission computed tomography
STAT3	Signal transducer and activator of transcription 3
TH	Tyrosine hydroxylase
TLR2	Toll-like receptor 2
TNFR1	Tumor necrosis factor receptor 1
TNF-α	Tumor necrosis factor-α
TUNEL	Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling
UPS	Ubiquitin proteasomal system
VMAT2	Vesicular monoamine transporter-2
WFI	Water for injection

List of Figures

List of Tables

Abstract

All current treatments of Parkinson's disease (PD) focus on enhancing the dopaminergic effects and providing symptomatic relief; however, they can neither delay the ongoing neurodegenerative process nor halt the disease progression. Filgrastim, a recombinant methionyl granulocyte colony-stimulating factor, displayed neuroprotective effects in many neurodegenerative and neurological diseases. This study aimed to assess the potential neuroprotective effects of filgrastim in rotenone-induced PD in rats; additionally, the potential underlying mechanisms of filgrastim actions were investigated. Rotenone (2 mg/kg/day, 28 days, *s.c.*) was used to induce PD in adult male Wistar rats. Filgrastim (20 or 40 µg/kg/day, *s.c.*) treatment was started one day before rotenone administration, continued concomitantly 6 h before rotenone administration, and extended for additional 7 days after the last rotenone dose. The effects of filgrastim on spontaneous locomotion, catalepsy, body weight, histology, and striatal dopamine (DA) content, as well as tyrosine hydroxylase (TH) and α-synuclein immunoreactivity were evaluated. Then, the effective filgrastim dose (40 µg/kg/day) was further tested for its potential anti-inflammatory, antiapoptotic, and neurotrophic actions. Filgrastim (40 µg/kg) prevented rotenone-induced behavioral deficits, weight reduction, striatal DA depletion, and histological damage. Besides, it significantly increased TH-positive neurons and reduced α-synuclein immunoreactivity in the midbrains and striata of rotenone-treated rats. These favorable effects were associated with the reduction of rotenone-induced neuroinflammation (a decrease in tumor necrosis factor-α and interleukin-1β levels and ionized calcium-binding adapter molecule-1 immunoreactivity) and inhibition of apoptosis (reduction of caspase-3 activity and Bax/Bcl-2 ratio). Moreover, filgrastim prevented rotenone-induced decline in brain-derived neurotrophic factor and ATP levels. Collectively, these results suggest that filgrastim might be a good candidate for management of PD in rats owing to its anti-inflammatory, antiapoptotic, and neurotrophic effects.

Keywords: Parkinson's disease, Filgrastim, Rotenone, Neuroinflammation, Apoptosis, BDNF