Neurotoxicity Research
https://doi.org/10.1007/s12640-018-9983-2

ORIGINAL ARTICLE

Rebamipide Mitigates Impairments in Mitochondrial Function and Bioenergetics with α-Synuclein Pathology in 6-OHDA-Induced Hemiparkinson's Model in Rats

Akanksha Mishra[1] · Sairam Krishnamurthy[1]

Received: 27 September 2018 / Revised: 16 November 2018 / Accepted: 22 November 2018

Abstract

Parkinson's disease (PD) is one of the widely reported neurodegenerative disorders affecting more than ten million people worldwide. Due to therapeutic limitations and several adverse effects associated with currently used drugs, it is crucial to search for safe and effective options for treatment of PD. Oxidative stress, mitochondrial dysfunction, α-synuclein oligomeric aggregates, and glucocerebrosidase (GCase) deficiency are involved in PD pathogenesis. Rebamipide, an anti-ulcer drug, is a proven free-radical scavenger and antioxidant. The drug has shown neuroprotective effects in cultured SH-SY5Y cells. Therefore, we investigated the pharmacological effect of rebamipide in 6-hydroxydopamine (6-OHDA)-induced experimental PD model. Rebamipide was given to adult male albino rats of Charles-Foster strain in 20, 40, and 80 mg/kg (R-20, R-40, and R-80) oral dose twice daily for 24 days (day 4 to day 27) after 6-OHDA intrastriatal injection. The drug inhibited 6-OHDA-induced motor deficits and nigral α-synuclein aggregates in dose-dependent manner. R-40 and R-80 dose dependently increased striatal mitochondrial complex I, II, IV, and V activities; mitochondrial bioenergetics; and nigral GCase activity. 6-OHDA-induced lipid peroxidation was decreased. Highest dose (R-80) also decreased apoptotic proteins and upregulated striatal dopamine concentration in 6-OHDA-induced hemiparkinson's rat model. Therefore, the anti-PD effect of rebamipide may involve stabilization of mitochondrial bioenergetics, enhancement of GCase enzymatic activity as well as decreased oxidative stress with α-synuclein pathology, and apoptosis in 6-OHDA-induced hemiparkinson's rat model. Hence, preclinical evidence indicates rebamipide to be a potential drug for management of PD.

Keywords Rebamipide · Mitochondrial bioenergetics · Oxidative stress · Parkinson's disease · α-Synuclein · Glucocerebrosidase

Abbreviations

4-MU	4-methylumbelliferone
6-OHDA	6-hydroxydopamine
α-Synuclein	alpha-synuclein
Aβ42	amyloid-β 1–42
ADP	adenosine diphosphate
ATP	adenosine triphosphate
β-actin	beta-actin
BSA	bovine serum albumin
CMC	carboxymethylcellulose
CNS	central nervous system
COMT	catechol-O-methyltransferase
DA	dopamine
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
ECD	electrochemical detector
EGTA	ethylene glycol-bis (β-aminoethyl ether) -N,N,N′,N′-tetraacetic acid
ELISA	enzyme-linked immunosorbent assay
ER	endoplasmic reticulum
ETC	electron transport chain
FAD	flavin adenine dinucleotide
FCCP	carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone
GC	glucocerebroside
GCase	glucocerebrosidase
h	hours
H^+	Hydrogen ion
H_2O_2	hydrogen peroxide

✉ Sairam Krishnamurthy
ksairam.phe@iitbhu.ac.in; saibliss@hotmail.com

[1] Neurotherapeutics Laboratory, Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, UP 221005, India

Published online: 04 January 2019