Progress in Neurobiology 94 (2011) 389–407

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

L-DOPA: A scapegoat for accelerated neurodegeneration in Parkinson's disease?

Janusz Lipski [a], Robert Nistico [b,c], Nicola Berretta [b], Ezia Guatteo [b], Giorgio Bernardi [b,d], Nicola B. Mercuri [b,d,*]

[a] Department of Physiology and Centre for Brain Research, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Rd., Auckland 1142, New Zealand
[b] Laboratory of Experimental Neurology, Fondazione Santa Lucia IRCCS, Via del Fosso di Fiorano 64, 00143 Rome, Italy
[c] Department of Pharmacobiology, University of Calabria, Via Pietro Bucci, 87036 Rende, Italy
[d] Neurological Clinic, University of Rome Tor Vergata, Viale Oxford 81, 00133 Rome, Italy

ARTICLE INFO

Article history:
Received 11 April 2011
Received in revised form 17 June 2011
Accepted 17 June 2011
Available online 24 June 2011

Keywords:
Levodopa
Dopamine
Toxicity
In vitro studies
In vivo animal studies
Clinical trials

ABSTRACT

There is consensus that amelioration of the motor symptoms of Parkinson's disease is most effective with L-DOPA (levodopa). However, this necessary therapeutic step is biased by an enduring belief that L-DOPA is toxic to the remaining substantia nigra dopaminergic neurons by itself, or by specific metabolites such as dopamine. The concept of L-DOPA toxicity originated from pre-clinical studies conducted mainly in cell culture, demonstrating that L-DOPA or its derivatives damage dopaminergic neurons due to oxidative stress and other mechanisms. However, the *in vitro* data remain controversial as some studies showed neuroprotective, rather than toxic action of the drug. The relevance of this debate needs to be considered in the context of the studies conducted on animals and in clinical trials that do not provide convincing evidence for L-DOPA toxicity *in vivo*. This review presents the current views on the pathophysiology of Parkinson's disease, focusing on mitochondrial dysfunction and oxidative/proteolytic stress, the factors that can be affected by L-DOPA or its metabolites. We then critically discuss the evidence supporting the two opposing views on the effects of L-DOPA *in vitro*, as well as the animal and human data. We also address the problem of inadequate experimental models used in these studies. L-DOPA remains the symptomatic 'hero' of Parkinson's disease. Whether it contributes to degeneration of nigral dopaminergic neurons, or is a 'scapegoat' for explaining undesirable or unexpected effects of the treatment, remains a hotly debated topic.

© 2011 Elsevier Ltd. All rights reserved.

Contents

Abbreviations: AADC, aromatic L-amino acid decarboxylase; ALDH, aldehyde dehydrogenase; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; AR, aldehyde reeductase; ATP, adenosine triphosphate; Bax, Bcl-2-associated X protein; BDNF, brain-derived neurotrophic factor; BSO, L-buthionine-sulfoximine; β-CIT, 2β-carbomethoxy-3β-(4-iodophenyl)tropane; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; cAMP, cyclic AMP; COMT, catechol-O-methyltransferase; CSF, cerebrospinal fluid; DA, dopamine; DAT, dopamine transporter; DAergic, dopaminergic; DOPAC, 3,4-dihydroxyphenylacteic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GDNF, glia-derived neurotrophic factor; JNK, c-Jun N-terminal kinase; LAT, l-aminoacid carrier; L-DOPA, levodopa or 3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MEA, multi-electrode array; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartic acid; NO, nitric oxide; $^{\bullet}O_2$, superoxide; $^{\bullet}OH^-$, hydroxyl radical; 6-OHDA, 6-hydrohydopamine; $^{\bullet}ONOO^-$, peroxynitrite; PD, Parkinson's disease; ROS, reactive oxygen species; RRF, retrorubral field; SNc, substantia nigra pars compacta; SOD, superoxide dismutase; TH, tyrosine hydroxylase; TOPA, 2,4,5-trihydroxyphenylalanine; UPS, ubiquitin-proteasome system; UPDRS, United Parkinson's Disease Rating Scale; VMAT, vesicular monoamine transporter; VTA, ventral tegmental area.

* Corresponding author at: Laboratory of Experimental Neurology, Fondazione Santa Lucia, Centro Europeo di Ricerca sul Cervello (CERC), Via del Fosso di Fiorano 64, 00143 Rome, Italy. Tel.: +39 06 501703317; fax: +39 06 501703307.
E-mail addresses: j.lipski@auckland.ac.nz (J. Lipski), robinistico@hotmail.com (R. Nistico), n.berretta@hsantalucia.it (N. Berretta), e.guatteo@hsantalucia.it (E. Guatteo), bernardi@uniroma2.it (G. Bernardi), mercurin@med.uniroma2.it (N.B. Mercuri).

0301-0082/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2011.06.005

1. Introduction

The progressive degeneration of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNc) leads to the motor symptoms of Parkinson's disease (PD) (e.g. Ehringer and Hornykiewicz, 1960; Olanow et al., 2009b; Schapira, 2009a). The resulting dramatic loss of dopamine (DA) in the striatum, the main projection field of these neurons, leads to insufficient stimulation of dopaminergic D1 (or D1-like) and D2 (D2-like) receptors and the classic symptomatic triad (resting tremor, bradykinesia, rigidity). Experimental and clinical data point at the involvement of mitochondrial dysfunction, oxidative stress, neuroinflammation, excitotoxicity and intracellular calcium dysregulation as the main causes of neurodegeneration. In addition, some genetic forms of PD (mainly in younger patients) result from mitochondrial dysfunction, misfolding of intracellular proteins or autophagy (see Section 2). There is also evidence for the involvement of environmental factors acting on mitochondria and causing profound and chronic derangement of the powerhouse of the DAergic neurons, due to alterations in the function of the respiratory chain and the excessive production of reactive oxygen species (ROS).

In spite of the fact that the culprit for neuronal degeneration has not been clearly identified, there are continuous experimental and clinical efforts to slow down or even stop degeneration and disease progression. Research has also been directed to identification and characterization of genes and proteins that control the development and survival of DAergic neurons. No cure has emerged yet, apart from the finding that monotherapy with the monoamine oxidase B (MAO-B) inhibitor rasagiline (1 mg/day) may result in slowing down the disease process (ADAGIO trial – Ahlskog and Uitti, 2010; Olanow et al., 2009a). Thus, in spite of the continuous effort to find a disease modifying therapy, neuroprotection in PD, as well as in other neurodegenerative diseases, still largely remains a myth (Löhle and Reichmann, 2010; Olanow, 2009; Schapira, 2009b). As a result, the most frequent current treatment strategy essentially aims at controlling the disabling motor symptoms of this relatively common (second after Alzheimer's disease) neurodegenerative disorder.

Although direct DA receptor agonists such as pramipexole or ropinirole are frequently used in treatment of PD, the most effective drug to elicit an improvement of the motor symptoms remains L-DOPA (3,4-dihydroxyphenylalanine; levodopa), regarded as the therapeutic 'gold standard' (e.g. Mercuri and Bernardi, 2005; Olanow et al., 2009b; Schapira, 2009a). However, during progressive treatment, L-DOPA becomes gradually less effective in ameliorating the motor symptoms (end of the 'honey moon' period) and various side effects develop. These include dyskinesias, dystonias, and shorter-lasting ON and longer-lasting OFF periods (ON – the period when the drug is effective; OFF – when it is ineffective). In fact, L-DOPA is not only the most potent drug in treating PD symptoms, but also in causing motor side effects (e.g. Fahn and the Parkinson Study Group, 2005; Holloway and the Parkinson Study Group CALM Cohort Investigators, 2009; Marsden and Parkes, 1977; Rascol et al., 2000).

There are different explanations as to why the side effects tend to occur more frequently after long-term treatment with L-DOPA than with DA receptor agonists. For example, an impaired reuptake of newly synthesized DA from L-DOPA, due to degeneration of DA terminals and the reduced activity of DA transporter (DAT) in the remaining terminals subject to oxidative stress (Berman et al., 1996), could determine an increase of the local extracellular concentration of this catecholamine (cf. Leenders et al., 1986). This, in turn, may lead to a rise in DA receptor occupancy (Chase and Oh, 2000; de la Fuente-Fernández et al., 2004) and overactivation of D1 receptors, believed to play a major role in inducing dyskinesias (e.g. Berthet and Bezard, 2009; Calabresi et al., 2010; Jenner, 2008). These receptors are overexpressed in the 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD, and their expression is further elevated during L-DOPA treatment (Rioux et al., 1997). On the other hand, L-DOPA-induced high levels of DA can downregulate or desensitize D2 receptors, resulting in shorter-lasting ON periods (Hurley and Jenner, 2006; Lee et al., 1978; but see Bordet et al., 1997).

However, based on the results demonstrating pro-oxidant and toxic properties of L-DOPA or its derivatives in pre-clinical studies (Sections 4 and 7.1), and on the outcomes of some clinical trials (Section 7.2), it has also been suggested that the side effects are due to a toxic action of the drug on the remaining DAergic neurons and to adaptive changes in the affected neural networks. According to this theory, L-DOPA promotes degeneration of nigral DAergic neurons by causing additional oxidative stress due to auto-oxidation products, and to increased DA content and turnover. The toxic theory of L-DOPA has been supported by the results of a large number of *in vitro* studies conducted with cell cultures, and by some animal experiments. These findings have not only sparked considerable debate among clinicians as to whether a similar mechanism operates in PD patients treated with the drug, but have also influenced the prescribing practice of some doctors who delay L-DOPA treatment and use other drugs first. Nevertheless, not all cell culture studies have reported toxic effects of L-DOPA, and in

Download English Version:

https://daneshyari.com/en/article/6286620

Download Persian Version:

https://daneshyari.com/article/6286620

Daneshyari.com