Neurochemistry International 62 (2013) 684–694

Contents lists available at SciVerse ScienceDirect

Neurochemistry International

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

Dopamine but not L-dopa stimulates neural glutathione metabolism. Potential implications for Parkinson's and other dopamine deficiency states

George F.G. Allen [a], Yasmin Ullah [b], Iain P. Hargreaves [a,c], John M. Land [a,c], Simon J.R. Heales [a,c,d,e,*]

[a] Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square House, Queen Square, London WC1N 3BG, UK
[b] Faculty of Pharmaceutical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark
[c] Neurometabolic Unit, National Hospital for Neurology and Neurosurgery, Box 105, Queen Square, London WC1N 3BG, UK
[d] Clinical and Molecular Genetics Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
[e] Chemical Pathology, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, UK

ARTICLE INFO

Article history:
Available online 19 December 2012

Keywords:
Dopamine
Reduced glutathione
Glutathione trafficking
Aromatic L-amino acid decarboxylase deficiency
L-Dopa
Antioxidant response elements

ABSTRACT

Dopamine is produced first by hydroxylalation of L-tyrosine to L-dihydroxyphenylalanine (L-dopa) and subsequently by the decarboxylation of L-dopa to dopamine catalysed by the enzymes tyrosine hydroxylase and aromatic L-amino acid decarboxylase (AADC) respectively. Reduced glutathione (GSH) acts as a major cellular antioxidant. We have investigated the role of dopamine in the control of GSH homeostasis in brain cells. The SH-SY5Y human neuroblastoma cell line was found to increase intracellular GSH levels in response to 50 μM dopamine treatment. Similarly the 1321N1 human astrocytoma cell line was found to increase GSH release in response to 50 μM dopamine. The same concentration of L-dopa was also found to increase intracellular GSH in SH-SY5Y cells, however when AADC was inhibited this affect was abolished. Furthermore 1321N1 cells which were found to have almost undetectable levels of AADC activity did not increase GSH release in response to 50 μM L-dopa. These results suggest that at these concentrations dopamine has the potential to act as a signal for the upregulation of GSH synthesis within neuronal-like cells and for the increased trafficking of GSH from astrocytes to neurons. This effect could potentially relate to the activation of antioxidant response elements leading to the induction of phase II detoxifying enzymes including those involved in GSH synthesis and release. The inability of L-dopa to produce a similar effect when AADC was inhibited or when AADC activity was absent indicates that these effects are relatively specific to dopamine. Additionally dopamine but not L-dopa treatment led in an increase in complex I activity of the respiratory chain in SH-SY5Y cells which may be related to the effect of dopamine on GSH levels.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

The monoamine neurotransmitter dopamine is involved in behavioural functions including the control of voluntary movement, working memory and motivation as well as in modulating the secretion of hormones such as prolactin (Caron et al., 1978; for review see Robbins and Everett, 2002). Dopamine is produced from L-tyrosine by sequential hydroxylation and decarboxylation steps producing first L-3,4-dihydroxyphenylalanine (L-dopa) and subsequently dopamine (see Fig. 1). These reactions are catalysed by the enzymes tyrosine hydroxylase and aromatic L-amino acid decarboxylase (AADC; Lovenberg et al., 1962; Nagatsu et al., 1964). AADC is also responsible for the production of serotonin (Lovenberg et al., 1962). The degradation of dopamine is catalysed by the enzymes monoamine oxidase and catechol-O-methyltransferase. Beyond this enzymatic degradation both dopamine and its precursor L-dopa are able to auto-oxidise producing first a semiquinone radical and subsequently a more stable quinone (see Pattison et al., 2002). These spontaneous oxidation reactions in the brain are thought to initiate the production of the pigment neuromelanin found in striatal dopaminergic neurons and noradrenergic neurons of the locus coeruleus (Wakamatsu et al., 2003).

The auto-oxidation of L-dopa and dopamine, that occurs readily in cell culture medium, produces reactive oxygen species (ROS) that may cause toxicity to neuronal cells in culture (Mena et al., 1993; Basma et al., 1995; Lai and Yu, 1997; Clement et al., 2002). However L-dopa administration *in vivo* is not for the most part

Abbreviations: L-dopa, L-3,4-dihydroxyphenylalanine; AADC, aromatic L-amino acid decarboxylase; BH4, tetrahydrobiopterin; ROS, reactive oxygen species; GSH, reduced glutathione; GSSG, glutathione disulphide; FBS, foetal bovine serum; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 3-OMD, 3-O-methyldopa; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; PKE, pig kidney epithelial; ARE, antioxidant response element; MRP1, multi-drug resistance protein 1; Nrf2, nuclear factor erythroid 2-related factor; keap1, kelch-like ECH associating protein 1; PLP, pyridoxal 5′-phosphate; DβH, dopamine β-hydroxylase; PNMT, phenolethanolamine N-methyltransferase; SAM, S-adensyl-methionine; SAH, S-adenosylhomocysteine.

* Corresponding author. Current address: Department of Chemical Pathology, Great Ormond Street Hospital, Great Ormond Street London, WC1N 1EH.
E-mail address: s.heales@ucl.ac.uk (S.J.R. Heales).

0197-0186/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuint.2012.12.004

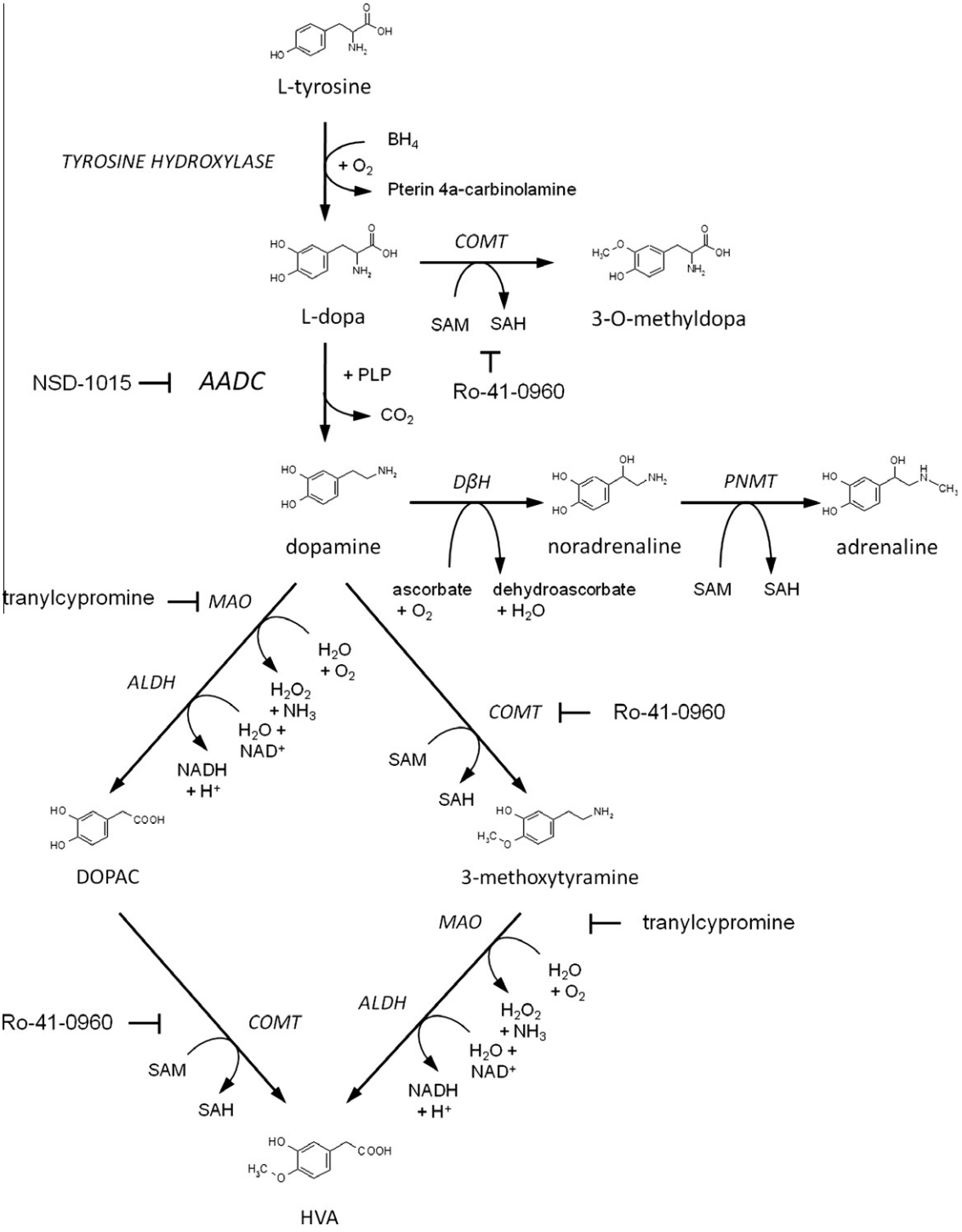

Fig. 1. Catecholamine metabolism and inhibitors of catecholamine metabolism. BH_4, tetrahydrobiotperin; AADC, aromatic L-amino acid decarboxylase; L-dopa, L-3,4-dihydroxyphenylalanine; PLP, pyridoxal 5′-phosphate; DβH, dopamine β-hydroxylase; PNMT, phenolethanolamine N-methyltransferase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; MAO, monoamine oxidase; ALDH, aldehyde dehydrogenase; COMT, catechol O-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid.

associated with neuronal toxicity (Mytilineou et al., 2003; Muller et al., 2004). Moreover in a neuronal-glial co-culture system L-dopa treatment does not lead to neuronal toxicity and glial-conditioned cell culture medium also protects against L-dopa induced toxicity (Mena et al., 1996, 1997a,b). Furthermore both L-dopa and dopamine at sub-toxic concentrations have been demonstrated to have some neuroprotective or neurotrophic effects (Han et al., 1996; Mena et al., 1997a; Jia et al., 2008). Pretreating cell cultures with either L-dopa or dopamine provided subsequent protection from cell death related to oxidative stress (Han et al., 1996; Jia et al., 2008). This neuroprotection may at least in part relate to increases in the intracellular levels of the antioxidant reduced glutathione (GSH) as treatment of cell cultures with either L-dopa or dopamine led to increases in GSH content (Mytilineou et al., 1993; Han et al., 1996; Mena et al., 1997a; Jia et al., 2008).

GSH synthesis is initiated by γ-glutamylcysteine ligase that produces the dipeptide γ-glutamylcysteine from glutamate and cysteine (Mandeles and Block, 1955). Subsequently glutathione

Download English Version:

https://daneshyari.com/en/article/10958091

Download Persian Version:

https://daneshyari.com/article/10958091

Daneshyari.com