Molecular Aspects of Medicine 30 (2009) 171–179

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Review

Oxysterols and neurodegenerative diseases

Ingemar Björkhem [a,*], Angel Cedazo-Minguez [b], Valerio Leoni [c], Steve Meaney [d]

[a] Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, 141 86 Huddinge, Sweden
[b] Neurotec Department, Karolinska Institutet, Karolinska University Hospital, 141 86 Huddinge, Sweden
[c] Division of Biochemistry and Genetics, "C.Besta" Neurological Institute, Milan, Italy
[d] School of Biological Sciences, Faculty of Science, Dublin Institute of Technology, Dublin, Ireland

ARTICLE INFO

Article history:
Received 22 December 2008
Accepted 10 February 2009

Keywords:
Blood–brain barrier
24S-Hydroxycholesterol
27-Hydroxycholesterol
β-Amyloid
Activity regulated cytoskeleton-associated protein
CYP27
CYP46

ABSTRACT

In contrast to their parent molecule cholesterol, two of its side-chain oxidized metabolites are able to cross the blood–brain barrier. There is a concentration-driven flux of 24S-hydroxycholesterol (24S-OHC) from the brain into the circulation, which is of major importance for elimination of excess cholesterol from the brain. The opposite flux of 27-hydroxycholesterol (27-OHC) from the circulation into the brain may regulate a number of key enzymes within the brain. *In vitro* experiments suggest that the balance between the levels of these two molecules may be of importance for the generation of β-amyloid peptides. In primary cultures of rat hippocampal cells 27-OHC is able to suppress expression of the activity regulated cytoskeleton-associated protein (Arc), a protein important in memory consolidation which is reduced in patients with Alzheimer's disease (AD). In the present work we explore the possibility that the flux of 27-OHC from the circulation into the brain represents the missing link between AD and hypercholesterolemia, and discuss the possibility that modification of this flux may be a therapeutic strategy. Lastly, we discuss the use of oxysterols as diagnostic markers in neurodegenerative disease.

Contents

* Corresponding author. Tel.: +46 8 58581235; fax: +46 8 58581260.
E-mail address: ingemar.bjorkhem@karolinska.se (I. Björkhem).

Abbreviations: 24S-OHC, 24S-hydroxycholesterol; 27-OHC, 27-hydroxycholesterol; Aβ, β-amyloid; ABCA1, ATP-binding cassette, subfamily A member 1; ABCG1, ATP-binding cassette, subfamily G member 1; AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid precursor protein; Arc, activity-regulated cytoskeleton-associated protein; CNS, central nervous system; CSF, cerebrospinal fluid; HDACi, histone deacetylase inhibitor; HMGCR, hydroxylmethyl-glutaryl coenzyme A reductase; LOAD, late onset AD; LXR, liver X receptor; MRI, magnetic resonance imaging; MS, multiple sclerosis; Nmdar, *N*-methyl-D-aspartate receptor.

0098-2997/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mam.2009.02.001

1. Brain cholesterol

1.1. General aspects

The brain is the most cholesterol-rich organ in the body and contains about 25% of the total amounts (for reviews, see Björkhem and Meaney, 2004; Dietschy and Turley, 2004). The major portion of this cholesterol is present in myelin, a lamellar arrangement of oligodendrocyte plasma membranes which acts as an electric insulator along the length of large axons. During early brain development, most of brain synthesis is associated with myelin production. Cholesterol seems to be of particular importance for the insulatory properties of myelin and there seems be a physiological imperative to maintain constant levels of this steroid in the brain. To achieve this, a highly efficient blood–brain barrier has been evolved that prevents exchange between cerebral and extracerebral pools of cholesterol. A direct consequence of this metabolic isolation has been the evolution of a very efficient cerebral cholesterol homeostasis, with minimal losses and extensive recycling. Apolipoprotein E (APOE) seems to be the most important mediator of this recycling process, but also other lipoproteins have been implicated, e.g. apolipoproteins J and D. The thrifty nature of cholesterol homeostasis in the brain is most probably a consequence of the low rate of *de novo* cholesterol synthesis in the adult brain, most of which is believed to occur in glial cells. Neurons are believed to have a very low rate of cholesterol synthesis and meet their cholesterol requirements via uptake of cholesterol carried in APOE-containing lipoproteins secreted from glial cells (Pfrieger, 2003).

Accumulating epidemiological and molecular evidence indicates that there is a clear link between cholesterol turnover and neurodegenerative diseases – hypercholesterolemia per-se is an important risk factor for Alzheimer's disease (AD) and Parkinson's disease and the presence of an APOE ε4 allele is the most well described genetic risk factor for late onset AD (LOAD). In addition, *in vitro* studies with cultured cells indicate that amyloid precursor protein (APP) present in cholesterol-rich membrane domains is more likely to undergo an initial cleavage by the β-secretase BACE-1. A subsequent cleavage by the φγ-secretase complex leads to the generation of β-amyloid (Aβ). In membranes with a low cholesterol content, α-cleavage seems to be favoured, resulting in products that do not form β-amyloid (Simons et al., 1998; Puglielli et al., 2003). In accord with the contention that cholesterol synthesis in the brain may be of regulatory importance for generation of amyloid, treatment with the statin class of cholesterol synthesis inhibitors, has been reported to have a preventive effect on neurodegeneration in some studies (Jick et al., 2000; Wolozin et al., 2000). Other studies have not been able to confirm this, however (Arvanitakis et al., 2008).

1.2. Side-chain oxidized oxysterols

The fact that there is a small synthesis of cholesterol in the adult brain implies that, in order to prevent cholesterol accumulation, there must be a corresponding excretion of cholesterol, or a metabolite, out from the brain. We have shown that the major mechanism for elimination of cholesterol from the mammalian brain is a conversion of cholesterol into the oxysterol 24S-hydroxycholesterol (24S-OHC), also known as cerebrosterol, which in contrast to cholesterol itself, is able to cross the blood–brain barrier (Lütjohann et al., 1996; Björkhem et al., 1997) (Fig. 1). The enzyme responsible for the production of 24-OHC is a species of cytochrome P-450, CYP46A1 (Lund et al., 1999). CYP46A1 is almost exclusively located to neuronal cells in the brain (Lund et al., 1999) and in the retina (Bretillon et al., 2007). In man the flux of 24S-OHC across the blood–brain barrier is about 6–7 mg/24 h (Lütjohann et al., 1996; Björkhem et al., 1998). In rats (Björkhem et al., 1997) and mice (Xie et al., 2003) the production of 24S-OHC has been shown to be equivalent to about two-thirds of the cholesterol

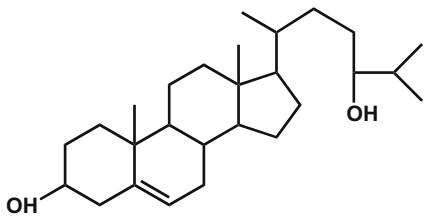

Fig. 1. Structure of 24S-hydroxycholesterol.