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Organelles in focus

Peroxisomes: The neuropathological consequences of peroxisomal dysfunction in the developing brain

Denis S. Barry*, Gerard W. O'Keeffe

Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

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ABSTRACT

Peroxisomes are intracellular organelles that perform vital metabolic functions. They have been extensively studied in the hepatic and renal systems, yet their pivotal roles in facilitating central nervous system patterning and in disease pathogenesis are only recently being firmly established by the neuroscience community. Peroxisomal functions including the break-down of long chain fatty acids, the removal of H_2O_2, and the biosynthesis of ether lipids. The build up of long chain fatty acids and H_2O_2 is detrimental to cellular function, and ether lipids play roles in maintaining cell membrane structure. These findings have major implications for treatments for the full spectrum of peroxisomal disorders. Here, we provide a timely review highlighting the most important data in recent times linking peroxisomal functions to brain formation, and we describe how peroxisomal deficiency and pathway dysfunction results in neurological deficits, the more severe of which result in life changing disabilities and death.

Organelle facts

- Peroxisomes are ubiquitous organelles and are enriched in neural tissues.
- Peroxisomes are more abundant in the brain during development (Ahlemeyer et al., 2007).
- Depending on the extent of the dysfunction, peroxisome disorders result in a range of neurological deficits, from mild mental disorders to severe motor dysfunction and mental retardation.
- Zellweger syndrome is the prototypical peroxisome biogenesis disorder and patients display abnormal neuronal migration patterns, which results in aberrant gyration of the cerebral cortex and abnormal foliation patterns in the cerebellum (Volpe and Adams, 1972).
- A selective lack of peroxisomes in neurons and astrocytes alone results in abnormal migration during development, while loss of peroxisomes from oligodendrocytes results in demyelination and axonal loss (Kassmann et al., 2007; Bottelbergs et al., 2010).
- Ether lipid depletion in the brain leads to reduced myelination, enlarged ventricles and cerebellar atrophy (Bams-Mengerink et al., 2006).

1. Introduction

Peroxisomes are single-membrane bound organelles found in all mammalian cells. They are recognised as playing key roles in essential metabolic processes, including the catabolism of very long chain fatty acids (VLCFAs) and the biosynthesis of ether-phospholipids (plasmalogens) and bile acids (Fig. 1) (Wanders et al., 2010). The importance of peroxisomal function in human health and disease came to light when the relationship between peroxisomal dysfunction and Zellweger syndrome (ZS; also known as cerebrohepatorenal syndrome) was first discovered (Goldfischer et al., 1973). Since this initial discovery, the elucidation of the molecular and genetic basis of ZS has revealed it is the most severe of the peroxisomal biogenesis disorders (PBDs). These are autosomal recessive metabolic diseases characterised by mutations in the *PEX* genes, which encode peroxin proteins (PEX) that are essential for peroxisome assembly and function (Fujiki et al., 2012). Of the PBDs, ZS is perhaps the most extensively studied and best understood. It is a rare, fatal disorder with an incidence of 1 in 50,000 live births and affected infants usually do not survive beyond the first year of life. Its pathology underlies an almost complete lack of peroxisomes and there is a multi-organ involvement. In particular, the nervous, hepatic and renal systems are affected, which reflects the ubiquitous presence and requirement for peroxisomes in mammalian cells (Fujiki et al., 2012).

In this review, we outline the importance of peroxisomal function for the normal development of the central nervous system (CNS). We review new data showing how peroxisomal agenesis and the resultant deficiencies in long chain fatty-acid catabolism

Abbreviations: CNS, central nervous system; DHA, docosaheaxanoic acid; MFP2, multifunctional protein two; PEX, peroxin protein; PBDs, peroxisomal biogenesis disorders; VLCFAs, very long chain fatty acids; ZS, Zellweger syndrome.

* Corresponding author. Tel.: +353 21 4202246; fax: +353 21 4273518.
E-mail addresses: d.barry@ucc.ie, denissbarry@gmail.com (D.S. Barry).

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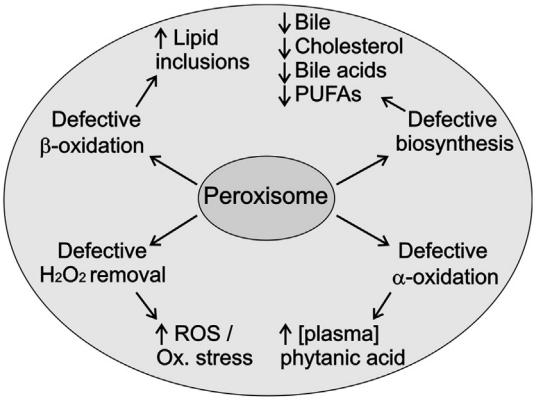

Fig. 1. The main cellular functions of peroxisomes. The metabolic consequences of peroxisomal dysfunction (VLCFA, very long chain fatty acids).

and plasmalogen biosynthesis lead to neuronal migration defects that may underlie the neonatal neurological deficits affecting the quality of life and lifespan of PBD patients.

2. Peroxisomal function in cells of the nervous system

Peroxisomes are members of the microbody family and are found in all eukaryotic cells, except erythrocytes. They play key roles in major metabolic pathways (Fig. 1), but are known mostly for their ability to: (1) break-down of VLCFAs through β-oxidation, and phytanic acid through α-oxidation, (2) detoxify hydrogen peroxide (H_2O_2) by peroxisomal catalase, and (3) perform the biosynthesis of ether-phospholipids, docosaheaxanoic acid (DHA), bile acids and cholesterol (Wanders and Waterham, 2006).

Recent experiments that have selectively removed peroxisomes from astrocytes, neurons and oligodendrocytes have revealed new functions for them in different neural cell types during CNS formation. Peroxisome deficient astrocytes (*GFAP-Pex5*$^{-/-}$) exhibited many lipid inclusions (Bottelbergs et al., 2010), which is suggestive of an intrinsic defect in β-oxidation. However, these lipid inclusions did not cause apoptosis or disrupt astrocyte functions, and *GFAP-Pex5*$^{-/-}$ mice lived a normal life span. Similarly, mice lacking peroxisomes from their neurons (*NEX-Pex5*$^{-/-}$) displayed normal patterns of myelination and neuronal migration (Bottelbergs et al., 2010). Collectively these data suggest that peroxisomal function in neurons and astrocytes may only have a minor involvement in metabolic processes during development (Kassmann et al., 2011). However, despite the lack of any major gross CNS malformations in mice with neurons and astrocytes deficient in peroxisomes, the loss of peroxisomes in oligodendrocytes (*CNP-Pex5*$^{-/-}$ mice) resulted in a range of major CNS pathologies including demyelination, lipid inclusions, axonal death, and inflammation (Kassmann et al., 2007). This suggests a fundamental role for peroxisomes in oligodendrocytes in the tropic support of developing neurons and their axons, while is supported by the enriched presence of peroxisomes at paranodes (Aubourg, 2007; Hulshagen et al., 2008).

3. Physiological roles of peroxisomes during CNS development

Peroxisomes are membranous organelles that contain over 60 oxidative enzymes, including the majority of a cell's catalase. Peroxisomes range in size from 0.1 μm to 1 μm in diameter, and their enzyme complement is adapted to the needs of different tissues and cell types. Their classical functions are in the anabolism of ether lipids and bile acids, and the catabolism of H_2O_2, and fatty acids, ensuring systemic levels are maintained within a healthy range for organ function (Fig. 1). A key consideration in peroxisomal biogenesis disorders is whether or not their neuropathologies are caused by accumulation of toxic metabolites intrinsic to brain cells or by metabolites in general circulation causing organ dysfunction first, and consequently brain dysfunction. Peroxisomes are particularly enriched in the liver and the brain early in life, and their numbers in the latter decrease into adulthood. Interestingly, conditional loss of peroxisomes from the liver results in major abnormalities in cerebral and cerebellar formation, whereas absence of CNS peroxisomes did not result in any gross cytoarchitectural abnormalities (Krysko et al., 2007), but did result in lipid accumulation, astrocytosis and disruption of the axon–myelin interface (Hulshagen et al., 2008). Unfortunately, our knowledge of exact peroxisomal function during CNS formation is limited somewhat by our lack of information regarding peroxisome distribution across CNS compartments and their dynamics during development.

4. Neuropathological hallmarks of PBDs

Due to their critical functions in vital organs, peroxisomal disorders can result in a range of pathologies (Table 1). These differ in severity depending on the extent of peroxisomal dysfunction. Defects include aberrant neuronal migration, dysmorphic facial features, cerebral hypotonia, epilepsy, cataracts, liver cirrhosis, renal cysts, and skeletal abnormalities. 25 peroxisome biogenesis disorders have been identified to date. ZS is the most severe of these and is usually fatal within the first year of life. Other PBDs caused by single peroxisomal enzyme defects include X-linked adrenoleukodystrophy, rhizomelic chondrodysplasia punctata, multifunctional protein two (MFP2) deficiency and infantile Refsum disease, and are usually fatal within the first 10–20 years of life. In ZS, the absence of peroxisomes from all organs leads to a range of neuropathologies (Table 1). These include abnormal brain gyration patterns, including perisylvian pachygyria with polymicrogyria in the adjacent frontoparietal areas of the cortex, most likely caused by delayed or defective neuronal migration and differentiation from the subventricular zone (Volpe and Adams, 1972; Powers and Moser, 1998). The cerebellum presents with the delayed formation of, or absence of fissures, microgyria and misplaced clusters of granule and Purkinje cells in the white matter (Faust, 2003; Krysko et al., 2007), most likely due to deficits in granule neuron numbers and absent migration cues. Furthermore, lipid accumulations are present in migrating neurons and radial glia in the cortex of Zellweger foetuses, yet radial glial morphology is unchanged (Powers et al., 1998). Moreover, ZS mice Purkinje cells develop axonal spheroids, in addition to dendrite and spine abnormalities (Muller et al., 2011). Neural cells of ZS neonates continue to degenerate postnatally. Taken together these data show how the absence of functional peroxisomes in the Zellweger CNS leads to the dysfunction of many of the basic cellular processes necessary to permit the normal migration of neurons and growth and maintenance of axons, dendrites and synapses.

4.1. The roles of specific peroxisomal enzymatic pathways in brain development

As described above, the precise relationships between the systemic and cellular biochemical abnormalities caused by aberrant peroxisomal functioning and altered brain cytoarchitecture are not yet fully resolved. MFP2 is a crucial component of the peroxisomal β-oxidation pathway and its deletion has major consequences for normal cellular metabolism and homeostatic lipid levels. Patients lacking MFP2 present with severe hypotonia, polymicrogyria and pachygyria, heterotopically positioned neurons in the cerebral and cerebellar cortex as well as regions of demyelination in the brain