Progress in Lipid Research 56 (2014) 1–18

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Phosphatidylserine in the brain: Metabolism and function

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ARTICLE INFO

Article history:
Received 23 April 2014
Received in revised form 18 June 2014
Accepted 21 June 2014
Available online 30 June 2014

Keywords:
Docosahexaenoic acid
Serine
Signal transduction
Membranes
Neuron
Cognition

ABSTRACT

Phosphatidylserine (PS) is the major anionic phospholipid class particularly enriched in the inner leaflet of the plasma membrane in neural tissues. PS is synthesized from phosphatidylcholine or phosphatidylethanolamine by exchanging the base head group with serine, and this reaction is catalyzed by phosphatidylserine synthase 1 and phosphatidylserine synthase 2 located in the endoplasmic reticulum. Activation of Akt, Raf-1 and protein kinase C signaling, which supports neuronal survival and differentiation, requires interaction of these proteins with PS localized in the cytoplasmic leaflet of the plasma membrane. Furthermore, neurotransmitter release by exocytosis and a number of synaptic receptors and proteins are modulated by PS present in the neuronal membranes. Brain is highly enriched with docosahexaenoic acid (DHA), and brain PS has a high DHA content. By promoting PS synthesis, DHA can uniquely expand the PS pool in neuronal membranes and thereby influence PS-dependent signaling and protein function. Ethanol decreases DHA-promoted PS synthesis and accumulation in neurons, which may contribute to the deleterious effects of ethanol intake. Improvement of some memory functions has been observed in cognitively impaired subjects as a result of PS supplementation, but the mechanism is unclear.

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Contents

Abbreviations: Akt, protein kinase B; DHA, docosahexaenoic acid; ERK, extracellular signal-regulated protein kinase; NAPE, *N*-acylphosphatidylethanolamine; PC, phosphatidylcholine; PDK1, phosphoinositide-dependent kinase-1; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine N-methyl transferase; PH, pleckstrin homology; PI3K, phosphatidylinositol 3-kinase; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PKC, protein kinase C; PS, phosphatidylserine; PSD, phosphatidylserine decarboxylase; PSS1, phosphatidylserine synthase 1; PSS2, phosphatidylserine synthase 2; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor.

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http://dx.doi.org/10.1016/j.plipres.2014.06.002
0163-7827/Published by Elsevier Ltd.

1. Introduction

Phosphatidylserine (PS) is the major acidic phospholipid class that accounts for 13–15% of the phospholipids in the human cerebral cortex [1]. In the plasma membrane, PS is localized exclusively in the cytoplasmic leaflet where it forms part of protein docking sites necessary for the activation of several key signaling pathways. These include the Akt, protein kinase C (PKC) and Raf-1 signaling that is known to stimulate neuronal survival, neurite growth and synaptogenesis [2–7]. Modulation of the PS level in the plasma membrane of neurons has significant impact on these signaling processes. The mechanism of PS-mediated activation of these neuronal signaling pathways is illustrated in Fig. 1.

In the synapses, PS plays an important role in exocytosis by influencing Ca^{2+}-dependent membrane fusion between synaptic vesicles and the target plasma membrane, which is mediated by synaptotagmin and soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex [8–11]. PS also modulates the AMPA glutamate receptor [12], interacts with synapsin I [13], and alters the conformation of the microtubule associated protein tau [14]. Furthermore, abnormal PS asymmetry in the synaptosomal membrane has been observed in mild cognitive impairment and Alzheimer's disease [15]. The recent discovery of the critical role of PS in activating important signal transduction pathways and modulating neurotransmitter release and receptor function as well as implications in neuropathophysiology have renewed interest in PS in relation to brain function.

This review focuses on the metabolism and function of PS in the nervous system. Further details can be obtained from previous reviews dealing with PS function in the mammalian brain [16], cell and molecular biology involved in PS metabolism [17], the synthesis and intracellular transport of PS [18,19], the effects of docosahexaenoic acid (DHA) on neuronal PS function [5], the interrelationship between phosphatidylethanolamine (PE) and PS metabolism [20–22], and the effects of PS on membrane properties [23].

2. Phosphatidylserine synthesis in the brain

In mammalian tissues, PS is synthesized from either phosphatidylcholine (PC) or PE exclusively by Ca^{2+}-dependent reactions where the head group of the substrate phospholipids is replaced by serine [20], as illustrated in Fig. 2. These base-exchange reactions are catalyzed by phosphatidylserine synthases (PSS) and so far two isoforms, PSS1 and PSS2 encoded by two separate genes, *Pss1* and *Pss2*, respectively, have been identified. PSS1 utilizes PC

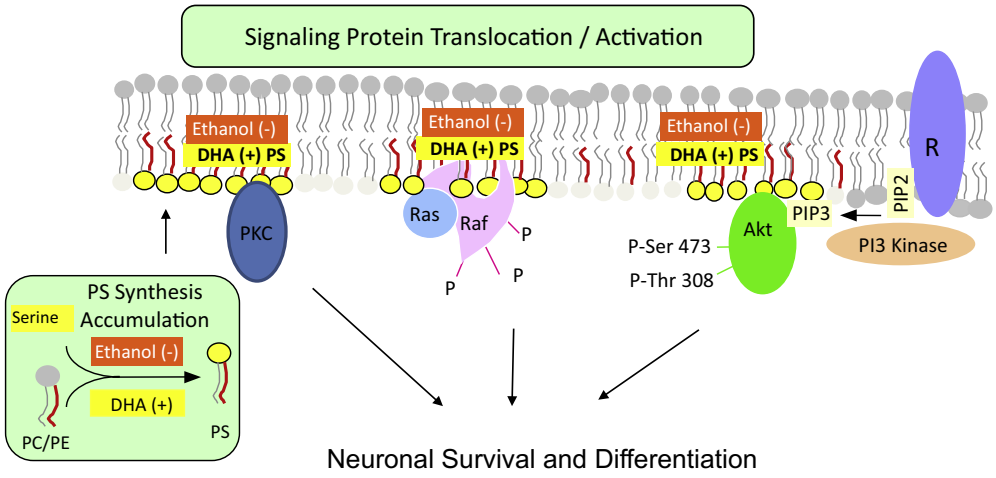

Fig. 1. Activation of neuronal signaling pathways facilitated by PS. Activation of Akt, protein kinase C and Raf-1 requires translocation from the cytosol to the cytoplasmic surface of the plasma membrane. Translocation is initiated by specific stimuli, for example, growth factor-dependent PIP_3 generation from PIP_2 by PI3 kinase in the case of Akt. Binding to the membrane occurs in part through an interaction of these proteins with PS present in anionic domains of the lipid bilayer, activating the signaling pathways leading to neuronal differentiation and survival. DHA facilitates this mechanism by increasing PS production in neurons, while ethanol has the opposite effect because it inhibits the DHA-induced increase in PS production. R: receptor.