Tissue-Specific Differences in Brain Phosphodiesters in Late-Life Major Depression

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Objective: *Late-life depression has been hypothesized to have a neurodegenerative component that leads to impaired executive function and increases in subcortical white matter hyperintensities. Phosphorus magnetic resonance spectroscopy (MRS) can quantify several important phosphorus metabolites in the brain, particularly the anabolic precursors and catabolic metabolites of the constituents of cell membranes, which could be altered by neurodegenerative activity.* **Methods:** *Ten patients with late-life major depression who were medication free at time of study and 11 aged normal comparison subjects were studied using ^{31}P MRS three-dimensional chemical shift imaging at 4 Tesla. Phosphatidylcholine and phosphatidylethanolamine comprise 90% of cell membranes in brain but cannot be quantified precisely with ^{31}P MRS. We measured phosphocholine and phosphoethanolamine, which are anabolic precursors, as well as glycerophosphocholine and glycerophosphoethanolamine, which are catabolic metabolites of phosphatidylcholine and phosphatidylethanolamine.* **Results:** *In accordance with our hypotheses, glycerophosphoethanolamine was elevated in white matter of depressed subjects, suggesting enhanced breakdown of cell membranes in these subjects. Glycerophosphocholine did not show any significant difference between comparison and depressed subjects but both showed an enhancement in white matter compared with gray matter. Contrary to our hypotheses, neither phosphocholine nor phosphoethanolamine showed evidence for reduction in late-life depression.* **Conclusion:** *These findings support the hypothesis that neurodegenerative processes occur in white matter in patients with late-life depression more than in the normal elderly population.* (Am J Geriatr Psychiatry 2013; ■:■−■)

Key Words: MRSI, ^{31}P MRS, elderly, aging, membranes

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INTRODUCTION

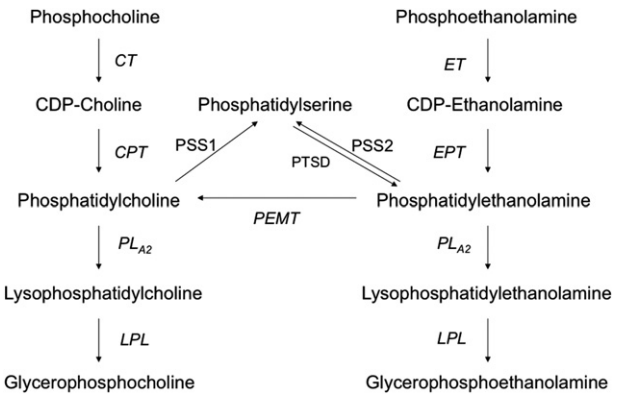
Biologic membranes serve numerous, essential cellular functions. Phosphatidylcholine and phosphatidylethanolamine are the two most prevalent membrane phospholipids, with each comprising approximately 45% of the central nervous system total membrane phospholipid pool.[1] Phosphorus magnetic resonance spectroscopy (^{31}P MRS) can quantify both anabolic precursors (phosphomonoesters [PMEs]) and catabolic metabolites (phosphodiesters [PDEs]) of these two important membrane phospholipids, giving insight into the state of membrane integrity and turnover.[2,3] The PMEs that can be resolved into independent peaks at 4-Tesla field strength are phosphocholine (PCho) and phosphoethanolamine (PEtn) and the PDEs that can be resolved are glycerophosphocholine (GPCho) and glycerophosphoethanolamine (GPEtn).

Phosphatidylcholine is synthesized directly via the cytidine diphosphate−choline pathway[4] from PCho. It can also be generated from phosphatidylethanolamine via phosphatidylethanolamine *N*-methyltransferase.[5,6] In an analogous manner, phosphatidylethanolamine can be synthesized from PEtn via the cytidine diphosphate−ethanolamine pathway (Fig. 1);[4] however, it cannot be directly synthesized from PCho because phosphatidylethanolamine *N*-methyltransferase only interacts with the phosphatidylethanolamine substrate.

Adult major depression has been characterized in studies using 1.5-Tesla ^{31}P MRS by increases in PME peak (composed mainly of PCho and PEtn) in frontal regions[7] but not in the basal ganglia.[8] However, the composition of the PMEs peak at 1.5 Tesla does include glycerol-3-phosphate and inositol phosphates, leaving some uncertainty as to which actual metabolite is increased in depression. Proton MRS findings in late-life depression include increased choline resonance (PCho and GPCho) in the basal ganglia[9] and reduced choline in the prefrontal cortex.[10]

Late-life depression has been hypothesized to have a vascular component,[11,12] yielding a condition characterized by lower cardiac health,[13] impaired executive dysfunction,[14,15] psychomotor retardation and apathy,[16] and treatment resistance to some antidepressants.[17,18] Magnetic resonance imaging findings in late-life depression include increased white matter hyperintensities[19] that are ischemic in nature[20] with concomitant microglial activation,[21] demyelination,[22] and other evidence of neuroinflammation. The volume of these ischemic lesions in patients with late-life depression significantly correlates with cognitive performance.[23] Reduced fractional anisotropy, as measured by diffusion tensor imaging,[24] has also been observed in patients with late-life depression. Taken together, these findings suggest that in late-life depression membrane integrity, particularly in white matter, may be compromised.

FIGURE 1. Biosynthetic pathways of phosphatidylcholine and phosphatidylethanolamine (Kennedy pathways). CT, CTP: phosphocholine cytidylyltransferase; ET, CTP: phosphoethanolamine cytidylyltransferase; CPT, CDP-choline:1, 2-diacylglycerol cholinephosphotransferase; PEMT: phosphatidylethanolamine N-methyltransferase; PTSD: phosphatidylserine decarboxylase; PSS: phsophatidylserine syntase; PLA_2: phospholipase A_2; LPL: lysophospholipase.



There are very large differences in the metabolic, functional, and neurodegenerative properties of gray and white matter.[25] Statistical methods have been developed that can incorporate information based on the segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) into the analysis of three-dimensional chemical shift imaging (3D-CSI) ^{31}P-MRS.[26−28] Making use of these methods, hypotheses unique to specific tissue classes, and relating to the metabolic differences between them, can be tested over the whole brain.

We performed a 3D-CSI ^{31}P MRS study at a 4-Tesla magnetic field strength measuring individual membrane metabolites in subjects with late-life depression versus normal comparison subjects. The following