Tissue Specific Changes in Brain Phosphodiesters in Late Life Major Depression

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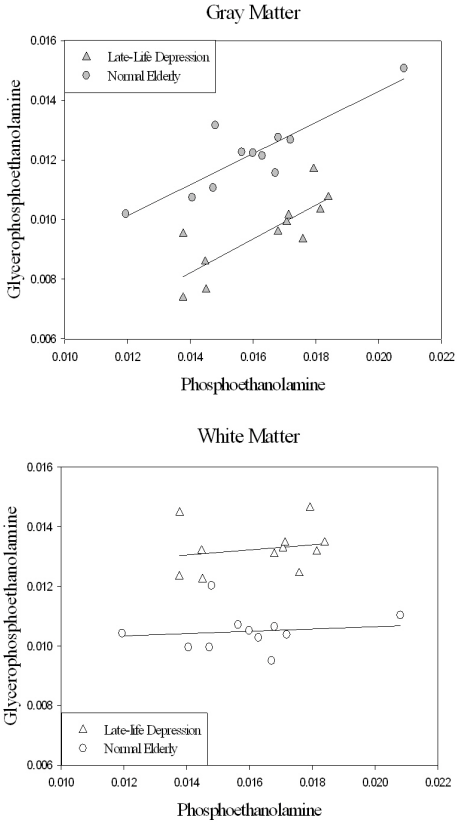
Biological membranes serve numerous, essential cellular functions including but not limited to maintaining cellular homeostasis, both for cells and subcellular organelles, intra and intercellular information processing and communication, as well as energy conversion tasks particularly mitochondrial oxidative phosphorylation (1). MRI findings in late life depression include increased white matter hyperintensities(2) and reduced fractional anisotropy as measured by diffusion tensor imaging(3) suggesting that membrane integrity, especially in white matter, may be compromised. We performed a 31P MRS study at a 4 tesla magnetic field strength and measured individual membrane metabolites in subjects with late-life depression versus normal elderly(4, 5). The following hypotheses were tested. Patients with late-life major depression would show an increase in PEtn and/or PCho consistent with the previous finding that phosphomonoesters were increased in major depression.(6, 7) We further hypothesized that the phosphodiesters (PDE), glycerophosphocholine (GPCho) and glycerophosphoethanolamine (GPEtn), particularly in white matter, will be increased in late-life major depression compared to normal elderly subjects reflecting increased membrane breakdown in the white matter. Finally we hypothesize that GPEtn will be distributed and altered fundamentally differently than GPCho due to the additional pathway of the inner mitochondrial membrane and that, of the PDE's, GPEtn will show changes in gray matter suggesting the possibility of mitochondrial dysfunction in the depressed subjects.

Methods

11 older adults and 11 healthy, non-depressed, non-demented adults, age $\geq$ 55, were recruited from local ads and the Geriatric Psychiatry Program, McLean Hospital. Depression subjects had been diagnosed with DSM-IV TR Major Depressive Disorder and had a Hamilton Depression Scale-17 item (HAMD17) $\geq$ 18. Subjects had a 31P-MRS scan at 4 Tesla (dual-tuned open face proton-phosphorus TEM whole-head coil). Phosphorus metabolites were recorded using a three-dimensional chemical shift imaging sequence. The extracted brain images were segmented into WM, GM and CSF, using FMRIB's Automated Segmentation Tool (FAST). Linear mixed effects models(8) were used to analyze the effects of late-life depression on phospholipid metabolite concentration in segmented brain tissue.

Results

Phosphocholine and phosphoethanolamine, the two phosphomonoesters measured in this study, did not differ between late life depression and normal elderly. Measured phosphocholine was significantly higher in white matter when compared to gray matter however there were no other significant differences in the quantity of metabolite measured between late life depression and controls when different tissue types were taken into account. Our final model for both phosphodiesters (GPCho and GPEtn) included significant adjustment for phosphoethanolamine and phosphocholine levels but not for age or sex. We observed an interaction between phosphoethanolamine and tissue type in our GPEtn model indicating that there was a significantly different influence of phosphoethanolamine in gray matter vs. white matter (Figure 1). There was a significant interaction of condition with gray matter and white matter such that gray matter GPEtn was lower in subjects with late life depression compared to normal elderly and white matter significantly elevated beyond levels seen in normal elderly in subjects with late life depression. In the final model, GPCho did not differ between late-life depression and normal elderly. However, similar to phosphocholine, there was a significant difference between gray matter and white matter glycerophosphocholine with white matter GPCho greater than gray matter in both controls and depressed subjects.



Discussion

These findings suggest that GPEtn is fundamentally altered in late-life depression with increases in white matter, possibly reflecting increased breakdown of phosphatidylethanolamine in white matter in late-life depression. GPEtn was also reduced in gray matter, when phosphoethanolamine level is accounted for.

Phosphatidylethanolamine, in the inner mitochondrial membrane, serves an essential function, and it is synthesized via a unique pathway, not involving phosphoethanolamine. Instead phosphatidylethanolamine in the inner mitochondrial membrane is synthesized from phosphatidylserine. This gray matter finding therefore would also support the hypothesis of mitochondrial dysfunction occurring in late life depression.

Bibliography

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