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Opinion Article

Post-Synaptic Proteome Targeting in Alzheimer's Disease with Psychosis

John George*, **Robert Kelvin**

Department of Pathology, University of California, Stockton, California, USA

DESCRIPTION

Individuals with Alzheimer's disease who develop psychotic symptoms (AD+P) experience faster cognitive and functional decline and lower synaptic integrity indicators than those who do not develop psychosis (AD-P). Psychotic symptoms occur in 40%-60% of Alzheimer's Disease (AD) patients. When compared to AD participants who do not have psychosis (AD-P), AD people who have psychosis (AD+P) had a faster cognitive deterioration. Prior to the onset of psychosis, there is greater cognitive impairment in the early stages of AD+P. Antipsychotics are currently used to treat psychosis in Alzheimer's disease, despite the fact that they are ineffective, do not reduce cognitive decline, and increase mortality. Furthermore, AD+P are associated with worse outcomes than AD-P, such as higher rates of aggression, caregiver distress, and functional deterioration and morality. As a result, there is a strong incentive to uncover the biology underpinning psychosis risk in AD in order to develop a more effective, successful treatment. Because synapse loss has long been recognized as the primary neuropathological sign of cognitive decline in Alzheimer's disease, it has been proposed that sensitivity to AD+P arises from more synaptic damage in AD+P than in AD-P.

Previous research comparing AD+P to AD-P subjects on a variety of indirect synapse integrity markers, such as grey matter volumes, cerebral glucose utilization or blood flow, or grey matter concentrations of the membrane breakdown products, glycerophosphoethanolamine and glycerophosphocholine, found support for this hypothesis in neocortical but not medial temporal regions. We recently examined grey matter levels of a small panel of 190 synaptic proteins in persons with AD+P and found reductions in canonical Postsynaptic Density (PSD) proteins when compared to AD-P subjects. These alterations overshadowed any differences in neuropathology load across groups or a decrease in the corresponding mRNA transcripts due to increased excitatory neuron loss in AD+P.

None of the prior studies looked specifically at the PSD in AD +P. As a result, we conducted a proteomic analysis of PSD fractions from the dorsolateral prefrontal cortex of a large sample of people with AD+P and AD-P, as well as a control group of cognitively normal elderly people. PSD protein levels in AD+P patients were considerably lower than in AD-P and comparative patients. PSDs from AD+P patients had amount of kinases, proteins regulating Rho GTPases, and proteins regulating the actin cytoskeleton than PSDs from AD-P patients. Finally, we used computational systems pharmacology to find new potential treatment candidates for AD+P based on PSD protein level differences between AD+P and AD-P.

The PSD proteome is characterized by extensive changes in AD +P. More testing of potential treatments in model systems is needed to determine their ability to reverse these modifications and reduce psychotic-like symptoms. The PSD proteome profile of AD+P revealed lower amounts of a network of kinases, proteins regulating Rho GTPases, and other actin cytoskeleton regulators. Maraviroc, a C-C Motif Chemokine Receptor 5 inhibitor, has been identified as a potential novel treatment.

We hypothesized that the PSD proteome differs between AD+P and AD-P, and that this proteomic signature could be used to identify novel pharmacotherapies. The risk of psychosis in Alzheimer's disease is largely genetic, with an estimated heritability of 60%, indicating a unique biologic vulnerability. Individuals with Alzheimer's disease who acquire psychotic symptoms (AD+P) have faster cognitive and functional deterioration and have lower indicators of synaptic integrity than those who do not develop psychosis (AD-P).

Correspondence to: John George, University of California, Stockton, California, USA, E-mail: johngeorge@yahoo.com

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