HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Biol Psychiatry. 2015 June 1; 77(11): 923–924. doi:10.1016/j.biopsych.2015.03.031.

Possible compensatory mechanisms for glutamatergic disconnection found in the auditory cortex in schizophrenia

Glenn T. Konopaske, M.D.[1,2] and **Joseph T. Coyle, M.D.**[1,2]

[1]Mailman Research Center, McLean Hospital, Belmont, MA, USA

[2]Department of Psychiatry, Harvard Medical School, Boston, MA, USA

In their excellent article published in this issue of *Biological Psychiatry*, MacDonald et al. (1) report on altered expression of proteins involved in glutamate signaling pathways in the primary auditory cortex of subjects with schizophrenia. In particular, they focused on protein co-expression that is inferred when the levels of different proteins are correlated across a cohort of subjects. In schizophrenia subjects, protein co-expression was found to be decreased overall. However, the co-expression of a small cluster of postsynaptic density proteins, unique to schizophrenia subjects, was surprisingly increased but correlated negatively with dendritic spine density.

Spines are highly dynamic structures, and the actin cytoskeleton plays a crucial role in their morphology and function. In the cell, actin exists in two forms: globular (G-actin) and filamentous (F-actin). G-actin is polymerized to form F-actin that is an important component of the actin cytoskeleton. Actin filaments are polarized, and unless capped by actin-capping proteins, undergo treadmilling with polymerization occurring at the barbed end and depolymerization at the pointed end. Several actin-binding proteins have been identified that regulate the length, cross-linking, stability and mechanical properties of actin filaments.

Synaptic activity has a profound impact on the generation and morphology of dendritic spines, and most excitatory glutamatergic neurotransmission occur at synapses localized to spines. Stimulation of N-methyl-D-aspartate (NMDA)-type glutamate receptors affects the formation of spines and their morphology by reorganizing the actin cytoskeleton (2). NMDA receptor activation also results in the trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA)-type glutamate receptors to dendritic spines (3). AMPA receptor stimulation causes the reorganization of the spine actin cytoskeleton and alteration of spine morphology (2). Maintenance of spines requires the persistent activation of AMPA receptors by spontaneously released glutamate (4).

MacDonald et al. utilized liquid chromatograph-selected reaction monitoring/mass spectrometry (LC-SRM/MS) to analyze 223 peptides generated from 155 proteins isolated from the auditory cortex from schizophrenia and control subjects. Functional annotation analysis using DAVID identified 4 proteins that were expressed differentially in schizophrenia and participate in glutamate signaling pathways. These proteins are GRIA3, GRIA4, ATP1A3, and GNAQ. GRIA3 and GRIA4 code for AMPA receptor subunits, and ATP1A3 is a sodium/potassium transporter involved in NMDA receptor function (5). Thus,

this study has identified alterations in glutamate signaling molecules in a brain area (e.g., auditory cortex) that exhibits dendritic spine loss.

In addition to protein expression analyses, MacDonald et al. also conducted protein co-expression analyses using an adaptation of the weighted gene co-expression network analysis (WGCNA) approach. In general, protein co-expression was reduced in schizophrenia subjects. However, a cluster of proteins, unique to the schizophrenia subjects, showed increased co-expression. This unique cluster was enriched with proteins involved in the cytoskeleton, synapses, and the postsynaptic density. In addition, there was a significant negative correlation between protein expression within this unique cluster and spine density in the auditory cortex in schizophrenia subjects. Thus, this study identified a unique cluster of proteins that might play a significant role in the pathophysiology of schizophrenia.

The study by MacDonald et al. has several important strengths. The authors used sophisticated techniques to analyze protein expression and rigorous models to assess functional analyses and protein co-expression. Schizophrenia and control subjects were well matched for age and other demographic variables. In addition, the post-mortem intervals (PMIs) were relatively low. The authors also attempted to control for the potential confound of antipsychotic medication treatment by measuring the protein expression of GRIA4, GRIA3, ATP1A3 and GNAQ in rhesus monkeys administered haloperidol or clozapine for 6 months.

In the Discussion section, the authors address the two major limitations of this study: cortical layer and cell type specificity. Spine loss was observed previously in the deep layer III of the auditory cortex (6). This study collected protein from tissue blocks containing all cortical layers. In addition, spine loss occurs chiefly on pyramidal cells in the auditory cortex, and this study included all cell types. As the authors suggest, proteomic analysis utilizing laser microdissection coupled with multiple label quantitative fluorescence microscopy would overcome these significant limitations. In addition to laminar and cellular specificity, future studies ought to include a cohort of subjects with bipolar disorder. Recently, dendritic spine loss was observed in the DLPFC deep layer III pyramidal cells from bipolar disorder subjects (7). Thus, dendritic spine loss might not be specific to schizophrenia, but rather a marker of severe psychopathology or perhaps, psychosis.

Although the reductions in dendritic length and in spine density in Golgi studies in schizophrenia may individually appear modest, the total reduction in glutamatergic synapses (spine density X dendritic length) is substantial, ranging from 20 to nearly 40 percent, depending on the study (6, 7). This loss of dendritic spines is consistent with the approximate 30 percent decrease in GRIA3 and 4 described in the auditory cortex by MacDonald et al. Using co-expression network analysis, they also observe a robust inverse relationship between spine density and a family of proteins that play a critical role in spine structure and function (i.e, two ankyrin 1 and 2, alpha1 spectrin and a vesicle recovery protein). A plausible explanation is that neurons attempt to compensate for the loss of excitatory synapses by increasing the functional and structural integrity of the remaining spines. Consistent with this interpretation, Hengen et al. have described homeostatic

mechanisms that maintain stable circuit activity by keeping neuronal function within a set-point range in spite of disrupted synaptic input (8).

Recent evidence supports NMDA receptor hypofunction as a related component of schizophrenia pathology with several schizophrenia susceptibility genes within one degree of separation from the NMDA receptor including serine racemase, which synthesizes the cortical NMDA receptor co-agonist, D-serine, and NR2A, a NMDA receptor subunit (9). Since activation of NMDA receptors promotes the incorporation of AMPA receptors into the synapse, the up-regulation of Gα(q), which mediates the effects of mGluR5 activation (5), could serve to enhance NMDA receptor function through its phosphorylation as another mechanism to partially overcome the loss of excitatory synapses. Thus, the alterations in glutamatergic signaling molecules in schizophrenia documented in this study may help explain the disorganized cortical neuronal activity observed in schizophrenia (10) but also highlight compensatory processes that might forestall a catastrophic collapse of cortical processing in the context of this substantial loss of glutamatergic synaptic connectivity in schizophrenia.

In summary, MacDonald et al. provide an elegant and technically sophisticated analysis of protein expression and co-expression related to dendritic spine loss in the auditory cortex from schizophrenia subjects. The study marshalls evidence for substantial reductions in glutamatergic neurotransmission in the auditory cortex and identifies a novel cluster of proteins whose expression negatively correlated with spine loss and may represent compensatory responses to the primary synaptic pathology.

Acknowledgments

This work was supported in part by NIH grants 1K08MH087640-01A1 (GTK), R01MH05190 and P50MH0G0450 (JTC). JTC reports consulting with Novartis, Forum Pharmaceuticals, AbbVie and Lilly in the last 3 years.

References

1. MacDonald ML, Ding Y, Newman J, Hemby S, Penzes P, Lewis DA, et al. Altered glutamate protein co-expression network topology linked to spine loss in the auditory cortex of schizophrenia. Biol Psychiatry. 2014
2. Halpain S, Hipolito A, Saffer L. Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. J Neurosci. 1998; 18:9835–9844. [PubMed: 9822742]
3. Shi SH, Hayashi Y, Petralia RS, Zaman SH, Wenthold RJ, Svoboda K, et al. Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation. Science. 1999; 284:1811–1816. [PubMed: 10364548]
4. McKinney RA, Capogna M, Durr R, Gahwiler BH, Thompson SM. Miniature synaptic events maintain dendritic spines via AMPA receptor activation. Nat Neurosci. 1999; 2:44–49. [PubMed: 10195179]
5. Schwendt M, McGinty JF. Regulator of G-protein signaling 4 interacts with metabotropic glutamate receptor subtype 5 in rat striatum: relevance to amphetamine behavioral sensitization. The Journal of pharmacology and experimental therapeutics. 2007; 323:650–657.
6. Glausier JR, Lewis DA. Dendritic spine pathology in schizophrenia. Neuroscience. 2013; 251:90–107. [PubMed: 22546337]
7. Konopaske GT, Lange N, Coyle JT, Benes FM. Prefrontal cortical dendritic spine pathology in schizophrenia and bipolar disorder. JAMA Psychiatry. 2014; 71:1321–1331.

8. Hengen KB, Lambo ME, Van Hooser SD, Katz DB, Turrigiano GG. Firing rate homeostasis in visual cortex of freely behaving rodents. Neuron. 2013; 80:335–342. [PubMed: 24139038]
9. Balu DT, Coyle JT. The NMDA receptor 'glycine modulatory site' in schizophrenia: d-serine, glycine, and beyond. Curr Opin Pharmacol. 2015; 20C:109–115. [PubMed: 25540902]
10. Galderisi S, Vignapiano A, Mucci A, Boutros NN. Physiological correlates of positive symptoms in schizophrenia. Curr Top Behav Neurosci. 2014; 21:103–128. [PubMed: 24920446]