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Research Report

Altered serine/threonine kinase activity in schizophrenia

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ABSTRACT

Converging evidence implicates alterations in multiple signaling pathways in the etiology of schizophrenia. Previously, these studies were limited to the analysis of one or a few phosphoproteins at a time. Here, we use a novel kinase array platform to simultaneously investigate the convergence of multiple signaling cascades implicated in schizophrenia. This technology uses consensus peptide substrates to assess activity levels of a large number (>100) of serine/threonine protein kinases. 19 peptide substrates were differentially phosphorylated (>15% change) in the frontal cortex in schizophrenia. These peptide substrates were examined using Ingenuity Pathway Analysis to group them according to the functions and to identify processes most likely affected in schizophrenia. Pathway analysis placed 14 of the 19 peptides into cellular homeostatic pathways, 10 into pathways governing cytoskeletal organization, and 8 into pathways governing ion homeostasis. These data are the first to simultaneously investigate comprehensive changes in signaling cascades in a severe psychiatric disorder. The examination of kinase activity in signaling pathways may facilitate the identification of novel substrates for drug discovery and the development of safer and more effective pharmacological treatment for schizophrenia.

1. Introduction

For decades the pharmacological treatment of severe mental illness has focused on modulation of neurotransmitter receptors. Compounds that activate or block receptors, transporters, or key enzymes are postulated to work by altering intracellular signaling cascades connected to these neurotransmitter systems, leading to symptom improvement via

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Table 1 – Summary published studies of phosphoproteins and protein kinases in schizophrenia.

Findings	Brain region	Brain Bank	Samples	Level of evidence	Reference
STEP61 ↑	ACC, DLPFC	Stanley Consortium, Mount Sinai Brain Bank	12 scz and 12 ctrl, 14 scz and 14 ctrl	Western	Carty et al. (2012)
PAK1 ↓, MLC ↑(ACC)↔(DLPFC), Cofilin 2 ↔	ACC, DLPFC	Mount Sinai Brain Bank	36 scz and 33 ctrl, 35 scz and 29 ctrl	Western	Rubio et al. (2012)
DARPP-32↓(II-V), phosphoDARPP-32↑(V)	DLPFC (layers II-V)	Fukushima Brain Bank	9 scz and 9 ctrl	Immunohistochemistry	Kunii et al. (2011a)
phosphoDARPP-32 ↑	STG	Fukushima Brain Bank	11 scz and 11 ctrl	Immunohistochemistry	Kunii et al. (2011b)
Casein Kinase II ↓, Syntaxin 1 ↓	BA10	Dallas Brain Collection	15 scz and 15 ctrl	Western	Castillo et al. (2010)
MAP2 ↓	BA9, BA32 (layers III and V)	Harvard Brain Tissue Resource Center	7 scz and 7 ctrl	Immunocytochemistry	Jones et al. (2002)
ERK1/2 ↑, phosphoERK ↔	PFC	Tokyo Metropolitan Matsuzawa Hospital	8 scz and 5 ctrl	Western	Swatton et al. (2004)
GSK3Beta ↓	FC	Rebecca L. Cooper Brain Bank	15 scz and 15 ctrl	Western	Amar et al. (2008)
phosphoCREB ↓	FC	Stanley Consortium	15 scz and 15 ctrl	Western	Kozlovsky et al. (2001)
Rap2 ↓, phosphoJNK1 ↓, phosphoJNK2 ↓, phosphoPSD95 ↓(ACC) ↑(DLPFC), Rack1 ↑, Fyn ↑, Cdk5 ↑	ACC, DLPFC	Mount Sinai Brain Bank	36 scz and 33 ctrl, 35 scz and 31 ctrl	Western	Funk et al. (2012)
phosphoGluN2B ↑	FC	Medical Research Council Brain Bank, Stanley Consortium	10 scz and 10 ctrl, 10 scz and 10 ctrl	Western	Emamian et al. (2004)
NRG1 ↔, ErbB4 ↔	BA9, BA10, BA46	Schizophrenia Research Center (University of Pennsylvania)	14 scz and 14 ctrl	Western	Hahn et al. (2006)

Abbreviations: anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), superior temporal gyrus (STG), Brodmann area (BA), prefrontal cortex (PFC), frontal cortex (FC), schizophrenia (scz), control (ctrl), increased (↑), decreased (↓), unchanged (↔).