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DISORDERS
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GROWTH FACTORS
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Contents

Symposium on Growth factors and psychiatric disorders, held at the Novartis Foundation, London, 20–22 March 2007

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This symposium is based on a proposal made by Moses Chao

Moses Chao  Chair’s introduction  1

Daniel C. Javitt  Phenomenology, aetiology and treatment of schizophrenia  4
Discussion  17

Jonathan Flint, Sagiv Shifman, Marcus Munafo and Richard Mott  Genetic variants in major depression  23
Discussion  33

Eero Castrén and Tomi Rantamäki  Neurotrophins in depression and antidepressant effects  43
Discussion  53

Jinbo Fan and Pamela Sklar  Genetics of bipolar disorder: focus on BDNF Val66Met polymorphism  60
Discussion  72

David A. Talmage  Mechanisms of neuregulin action  74
Discussion  84

General discussion I  87

H. Akil, S. J. Evans, C. A. Turner, J. Perez, R. M. Myers, W. E. Bunney, E. G. Jones, S. J. Watson and other members of the Pritzker Consortium  The fibroblast growth factor family and mood disorders  94
Discussion  97
Jay N. Giedd, Rhoshel K. Lenroot, Philip Shaw, Francois Lalonde, Mark Celano, Samantha White, Julia Tossell, Anjene Addington and Nitin Gogtay  Trajectories of anatomic brain development as a phenotype 101
Discussion 112

Bai Lu and Keri Martinowich  Cell biology of BDNF and its relevance to schizophrenia 119
Discussion 129

Enrico Tongiorgi and Gabriele Baj  Functions and mechanisms of BDNF mRNA trafficking 136
Discussion 147

Amar Sahay and René Hen  Hippocampal neurogenesis and depression 152
Discussion 160

Andrés Buonanno, Oh-Bin Kwon, Leqin Yan, Carmen Gonzalez, Marines Longart, Dax Hoffman and Detlef Vullhorst  Neuregulins and neuronal plasticity: possible relevance in schizophrenia 165
Discussion 177

Zhe-Yu Chen, Kevin Bath, Bruce McEwen, Barbara Hempstead and Francis Lee  Impact of genetic variant BDNF (Val66Met) on brain structure and function 180
Discussion 188

General discussion II  193

D. Malaspina, M. Perrin, K. R. Kleinhaus, M. Opler and S. Harlap  Growth and schizophrenia: aetiology, epidemiology and epigenetics 196
Discussion 203

Luiz M. Camargo, Qi Wang and Nicholas J. Brandon  What can we learn from the disrupted in schizophrenia 1 interactome: lessons for target identification and disease biology? 208
Discussion 216
Participants

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Chair’s introduction

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Psychiatric disorders such as depression, bipolar disease and schizophrenia are debilitating mental illnesses that are influenced by many genetic and environmental factors. While little is known about the neural circuits that underlie mood disorders, genetic studies in the last three years have identified several growth factors as susceptibility genes for depression and schizophrenia, as well as learning and memory disorders. One common theme is that these disorders reflect dysregulation of neural plasticity, as well as neurodevelopment. This symposium on growth factors and psychiatric disorders will consider the pathophysiology and genetics of schizophrenia and depression, and will discuss how growth factors such as neurotrophins and neuregulins may alter synaptic plasticity on a molecular and neural systems level.

I wish to start with a historical footnote. A few weeks ago, Tom Eagleton, a prominent politician, passed away. In 1972, he ran as the vice presidential nominee with George McGovern. Eagleton was asked to step down because it was disclosed that he had suffered several bouts of serious depression. One of the comments made by McGovern in an obituary in the *New York Times* was that that no one in the 1970s knew anything about mental illness, including himself. McGovern had asked Eagleton to leave the ticket, and then lost the general election to Nixon. Over the last 35 years, much progress has been made in biomedical research, including the advent of molecular biology and the sequencing of the entire human genome. Many new insights have been generated from molecular genetics that are relevant to psychiatric disorders.

This meeting presents an opportunity to bring three different groups together: the psychiatric community, basic neuroscientists and human geneticists. These groups rarely encounter each other at meetings. The goal is to encourage cross-fertilization of these disciplines in a small, focused conference. The format of a Novartis Foundation symposium offers an excellent opportunity to foster multidisciplinary interactions that will generate new approaches to this increasingly important topic.

The rationale for this meeting came from the realization that many complex psychiatric disorders have a genetic basis. This has been suggested by a growing
number of association and linkage studies. Also, it has become clear that there are clear links to growth factors and their receptors. We will discuss the role of growth factors at length in this meeting, in particular brain-derived neurotrophic factor (BDNF) and neuregulins and their tyrosine kinase receptors, as well as members of the fibroblast growth factor (FGF) family. It is also worth noting that one of the major hypotheses to account for psychiatric illnesses is from neurodevelopmental and genetic contributions; another comes from changes in synaptic plasticity. These activities are inherent in the actions of growth factors. I am certain these themes will emerge in the papers at this meeting. The challenge for the participants is to determine the strength of these hypotheses.

My interest in this area stems from work on neurotrophic factor receptors, particularly the nerve growth factor (NGF) family, but BDNF has garnered much attention over the last few years. The original identification and cloning of BDNF was done by Yves-Alain Barde (Leibrock et al 1989). It took Yves Barde’s group many years to purify the BDNF protein and to identify the gene. This trophic factor was originally identified for its trophic and differentiation properties, but it also possesses other biological activities. In the last 10 years it has become clear that BDNF exerts dramatic effects upon synaptic transmission in an activity-dependent manner, both on the presynaptic and postsynaptic sites of the synapse. This is an exciting area of research, as there are several strong connections to psychiatric disease. There are two seminal papers in this area. The first is by Eric Lander and Pam Sklar, who identified BDNF as a potential risk locus for bipolar disorder (Sklar et al 2002). A year later, Daniel Weinberger and Bai Lu (Egan et al 2003) characterized the same polymorphism in the context of BDNF release and episodic memory in human subjects. These findings set the stage for a growing number of studies on BDNF and human behaviour.

The other finding that had an important impact on the field of psychiatry came from studies on neuregulin. Kári Stefánsson and deCODE published the original observation that proposed neuregulin as a potential risk factor for schizophrenia (Stefánsson et al 2002). When this paper was published, there was scepticism about how polymorphisms in neuregulin were related to schizophrenia. Since this finding, there has been considerable attention on this issue in other populations. Many single nucleotide polymorphisms in neuregulin 1 have now provided strong genetic evidence in many diverse human populations, including Irish, Scottish and Chinese. This analysis has been complicated because the gene is very large and produces many splice variants and isoforms derived from multiple processing events. As a result, there are a large number of neuregulin proteins with different functions. The history of this protein is complex: it was designated by at least five different names. These names indicate that neuregulin proteins possess many activities, ranging from glial growth, neuronal migration, synapse formation and myelination. In this meeting, we will define several of the functions of this inte-
resting family of proteins, which are directly relevant to the development of psychiatric illnesses.

BDNF and neuregulin are of considerable interest, but many other growth factors display similar activities and functions. I hope we can also consider these other growth factor activities. In terms of the main questions that should be considered at this meeting, the first is how strong is the evidence that growth factors and trophic factors are involved in psychiatric diseases? The mechanism of action of growth factors in psychiatric illnesses has not been explored yet, but if we consider the common signalling mechanisms of tyrosine kinase receptors, the question arises whether other growth factors are also involved in psychiatric disorders? This raises the question of specificity: do only a few trophic factors have an impact upon mental illnesses, or do they all participate in some way?

Another unanswered question concerns pharmacological treatments with antidepressants and other psychotropic drugs. Many antidepressants and psychotropic drugs require a long period of time to become efficacious. Why? BDNF levels are increased by antidepressants, but this time course differs from the clinical time course. Finally, since many of the drugs that have been introduced in the last few years are derived from previous drugs (there have been very few new pharmacological approaches), can we use the information from cellular mechanisms and signal transduction to design new approaches and new drugs for psychiatric illnesses?

The meeting will be primarily devoted to growth factors and trophic factors, and their relevance to psychiatric illnesses, but there are many other genes and proteins that have been implicated in these illnesses. During the course of the symposium we will consider some of the most relevant candidates. I hope that the topic of growth factors will act as a probe into the study of psychiatric illnesses, and that the information will be integrated to provide insights into future treatment for mood disorders.

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