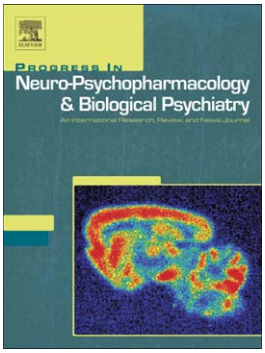
Accepted Manuscript



Molecular neurobiology of major depressive disorder

Yong-Ku Kim

PII: S0278-5846(15)00143-8
DOI: doi: 10.1016/j.pnpbp.2015.07.004
Reference: PNP 8803

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Please cite this article as: Kim Yong-Ku, Molecular neurobiology of major depressive disorder, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2015), doi: 10.1016/j.pnpbp.2015.07.004

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

-Preface-

Molecular neurobiology of major depressive disorder

Depression is a heterogeneous syndrome comprising numerous diseases of distinct causes and pathophysiologies. Recently, several promising hypotheses of depression and antidepressant action have been formulated. These hypotheses are largely based on dysregulation of neural plasticity, CREB, BDNF, corticotropin-releasing factor, glucocorticoid, hypothalamic-pituitary adrenal axis, and cytokines. Recent work has revealed that several brain regions, such as the hippocampus, prefrontal cortex, amygdala, nucleus accumbens, and other hypothalamic nuclei, are involved in the neural circuit of depression. The brain regions are critical in regulating memory, mood, motivation, sleep, eating, circadian rhythm, and responses to rewarding and adverse stimuli, which are all abnormal in depressed patients. Depression is not likely to result from a single gene or a single external event, but appears to be caused by a complex interaction between genes and the environment in susceptible persons. Until now, a gene or series of genes that causes depression has not been identified. However, certain genes are clearly risk factors for developing depression, increasing the likelihood that severe environmental stress will precipitate the onset of this disease. Thus, a combination of genetics, early life stress, and ongoing stress may ultimately determine individual responses to stress and vulnerability to depression. Increased understandings of gene–environment interactions in the pathophysiology of depression lead to advancement in personalized medicine by means of genotyping for inter-individual variability in drug action and metabolism. Gene–environment interactions may explain why some subjects become depressed while others remain unaffected.

The aim of the special issue is to enlarge current knowledge of depression from the perspectives of neurobiology, molecular genetics, molecular neuroimaging, neuroimmunology, and animal models of depression. In this issue, Dwivedi reviews the pathogenetic and therapeutic implications of microRNAs (miRNAs) in major depressive disorder. This is an outstanding and provocative review describing the role of miRNAs in the regulation of gene expression in depressed individuals.

ACCEPTED MANUSCRIPT

Importantly, he describes miRNAs as targets of antidepressants and ECT. Because miRNAs are present in circulating blood and can be easily detected, they can be used as diagnostic and therapeutic tools to make diagnosis of depression more objective, reliable, and predictable. Deutschenbaur et al. describe the mechanisms and functions of glutamate and related receptors and introduce newly developed or applied drugs acting on the glutamatergic system and having an antidepressant effect. Drugs targeting the glutamatergic system open up a promising new territory for the development of drugs to meet the needs of patients with major depression. Lin and Tsai review genome-wide gene expression analyses (with RNA derived from peripheral blood) in depressed patients, describing case/control approaches and alterations associated with treatment outcomes. Modeling tools based on clinical factors, such as gene expression data, may help patients and doctors make more informed and personalized decisions. Czeh et al. provide an elegant overview of the various animal models that are used most commonly for depression, and discuss their advantages and limitations. They describe genetic models, including the recently developed optogenetic tools, and stress models, such as the social stress, chronic mild stress, learned helplessness, and early-life stress paradigms. Animal models based on environmental or social stressors will be highly relevant for research aiming to understand the underlying pathophysiology of major depression in the future. Won and Ham provide a comprehensive review of available imaging genetics studies on monoaminergic genes with regard to specific brain structures. Imaging genetics applies anatomical or functional imaging technologies as phenotypic assays to evaluate genetic variations and their impact on behavior. The specific selection of genes (SLC6A4, MAOA, TPH2, HTR1A, COMT) and brain regions (hippocampus, amygdala, anterior cingulate cortex, orbitofrontal cortex) in this review seems appropriate, because variations in monoaminergic genes have repeatedly been suggested to influence brain areas involved in emotion processing and to render it susceptible to depression. Rantamaki and Yalcin provide and hypothesize important insights into the neurobiological mechanisms of classical antidepressants and rapid-acting antidepressants, particularly ketamine. They carefully discuss the effects of antidepressants at the molecular and neural network levels. Better understanding of the neurobiological effects of diverse

ACCEPTED MANUSCRIPT

antidepressant treatments on neuronal connectivity and function will lead to more effective therapeutic approaches against major depression and other nervous system disorders that benefit from induced plasticity. Recent advances in epigenetics have led to the realization that chromatin remodeling mediated by histone deacetylase (HDAC) is closely involved in the regulation of gene transcription. In this context, Fuchikami et al. review the efficacy of HDAC inhibitors in preclinical studies and treatment-resistant depression. Since newer HDAC inhibitors with less toxicity have been developed for use in cancer therapy, these drugs may also hold promise for the pharmacotherapy of antidepressant-resistant depression. Kim et al. describe the critical role of pro-inflammatory cytokines in neuroinflammation, the HPA axis, and depression. In brief, chronic neuroinflammation inhibits hippocampal glucocorticoid (GR) function, which in turn exacerbates pro-inflammatory cytokine activity and aggravates chronic neuroinflammation. Conversely, neuroinflammation causes an imbalance between oxidative stress and the antioxidant system, which is also associated with depression.

I would like to thank all of the contributors for their valuable time spent preparing manuscripts. I believe that increasing understanding of the neurobiological processes of depression will fundamentally improve the treatment and prevention of that illness.

Yong-Ku Kim, MD, PhD

Professor

Department of Psychiatry

College of Medicine

Korea University

Republic of Korea

yongku@korea.ac.kr