



PROGRESS IN NEUROSCIENCE PINS



Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&

The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 1/16/13, 4 PM, coffee at 3:45 PM
Weill Auditorium

Transcriptional and Epigenetic Mechanisms of Depression

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Abstract:

Depression is a common, chronic, and debilitating disease. Although many patients benefit from antidepressant medications or other therapies, only about half show complete remission. Factors that precipitate depression, such as stress, are incompletely understood.

We have used chronic social defeat stress as an animal model of. Prolonged exposure to an aggressor induces lasting changes in behavior such as social avoidance and anhedonia-like symptoms, which are reversed by chronic (but not acute) treatment with available antidepressants. Roughly one-third of mice subjected to social defeat stress do not exhibit these deleterious behaviors and appear "resilient." We are exploring the molecular basis of defeat-induced behavioral pathology, antidepressant action, and resilience by analyzing genome-wide changes in gene expression and chromatin modifications in several limbic brain regions. One area of focus is the nucleus accumbens, a key brain reward region implicated in aspects of depression.

We have identified sets of genes that remain altered one month after defeat stress. Many of these changes are reversed by chronic antidepressant treatment. Interestingly, a large subset of these genes, whose abnormalities are corrected by antidepressants, appear normal in resilient mice. These findings suggest that antidepressants work in part by inducing changes in gene and chromatin regulation in nucleus accumbens that occur naturally in more resilient individuals. Current studies are underway to investigate the genes and molecular pathways involved in these various responses. Specific genes that control susceptibility, resilience, and antidepressant responses will be discussed.

Together, this work provides novel insight into the molecular mechanisms by which chronic stress produces lasting changes in specific brain areas, and associated changes in the functioning of neural circuits, to cause depression-like symptoms. The findings also suggest novel leads for the development of new antidepressant treatments.



Recent relevant publications:

Wilkinson, M.B., Dias, C., Magida, J., Mazei-Robison, M., Lobo, M.K., Kennedy, P., Dietz, D., Covington, H. III, Russo, S., Neve, R., Ghose, S., Tamminga, C., and Nestler, E.J. (2011) A novel role of the WNT-Dishevelled-GSK3b signaling cascade in the mouse nucleus accumbens in a social defeat model of depression. *J. Neurosci.* 31:9084-9092.

Vialou, V., Feng, J., Robison, A.J., and Nestler, E.J. (2012) Epigenetic mechanisms of depression and antidepressant action. *Annu. Rev. Pharmacol. Toxicol.* 53:59-87.



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