

Ketamine and Imipramine Reverse Transcriptional Signatures of Susceptibility and Induce Resilience-Specific Gene Expression Profiles

Biological Psychiatry; June 2016

Bagot RC, Cates HM, Purushothaman I, Vialou V, Heller EA, Yieh L, LaBonté B, Peña CJ, Shen L, Wittenberg GM, Nestler EJ.

Objective - Currently-used antidepressants are not effective in everyone with depression; hence, the need to find novel therapeutic targets is urgent. Depression treatment and research is complicated because subjects respond differently even when exposed to similar chronic stress. Also, individuals respond differently to antidepressants. Hence, it seems plausible that there might be genetic factors at play. In this paper, the authors looked at a genetic process known as transcription.

Transcription is the first step in gene expression, and is the process by which a segment of DNA is copied into RNA. The resulting RNA can be then used either as a blueprint for protein synthesis as it has all the necessary information, or can itself be the end product.

Response of experimental animals to chronic stress (which can cause depression) can change transcription, and it has been shown that antidepressants can reverse this phenomenon. With this background in mind, the authors of this study explored transcriptional profiles in four parts of the brain that are critical for depressive behavior. Mice were subject to an experimental paradigm known as the chronic social defeat stress and RNA-sequencing was done to find differences in transcription in response to two antidepressants. The hope was that doing a comprehensive survey of the transcriptional profiles in response to existing antidepressants might give clues about their mechanism of action on a genetic level. Ultimately, this information could be used to find better and more effective therapies. The chronic social defeat stress model is widely used by researchers to study depression. After being subject to this model, animals can be divided into either being resistant to depression, or being susceptible. The authors wanted to learn the basis of resilience by studying the transcriptional profiles of mice that did not exhibit depressive behavior (i.e. the depression-resistant mice).

Results – There were clear differences in the pattern of transcription between mice that showed depressive behavior after chronic social defeat stress vs. those that showed resilience. An advantage of this study was the discovery of candidates that hadn't been previously thought to be important in depressive behavior. For example, genes known as *Dkk1* and *Neurod2* were revealed to control depression susceptibility in structures of the brain known as the ventral hippocampus, and the nucleus accumbens.

Interpretation – This study provides a first step and a resource for transcriptional changes in depression. The next step would be to select promising candidates out of this study, and perform targeted experiments on experimental animals. Ultimately, the goal is to provide leads for drugs that can be used in people with depression.

Link to the paper – Free access – no

Short bio

This summary was written by Sloka Iyengar, PhD- a neuroscientist, science writer, and healthcare consultant based in New York (Jan 2017).

Long bio

Sloka S. Iyengar, PhD is a neuroscientist, and has been investigating mechanisms that cause neurons to generate and sustain spontaneous seizures. For her graduate work, Sloka used electrophysiology to study epileptic circuits; as a postdoctoral fellow, she studied neurogenesis

(the birth of new neurons in the adult brain) in the hippocampus. She also conducted clinical trials for people with epilepsy. Sloka is also a science writer and contributes regularly to websites to make neuroscience research more accessible to non-scientists. She also advocates for increased neuroscience funding on Capitol Hill. Presently, she works as a healthcare consultant at Boston Strategic Partners. She is a professional dancer, and loves to swim, and embroider.