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Comparative Transcriptomic Analysis of the Effects of Antidepressant Drugs in Stress-Susceptible Mice

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As major depressive and bipolar disorders continue to be leading causes of disability worldwide (1), there is an urgent need for more effective treatments and better understanding of the mechanisms of actions of classical and novel classes of antidepressants. For the past 60 years, the treatment of depression has relied on pharmacological targeting of monoaminergic neurotransmission. This approach, however, has yielded limited efficacy, with over 50% of patients failing to achieve full remission (2), while weeks to months often pass before symptoms subside in those who do respond—which poses a marked risk for suicidal patients in particular. Over the past decade, there has been great excitement in the field of psychiatry, as numerous clinical studies have shown that ketamine, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, can induce rapid antidepressant effects in treatment-resistant individuals (3,4), with concomitant reduction of suicidal ideation in a subset of these patients (5).

Animal models have been paramount to dissecting potential mechanisms implicated in the therapeutic effects of classical and novel antidepressants. One such model, which is used in the study by Bagot *et al.* (6), is chronic social defeat stress. This stress draws its strength from an ethological and ecological validity in that repeated exposure to social defeat generates persistent emotional stress without habituation (7), and most animals exposed to this stress respond to chronic, but not acute, classical antidepressant treatments (8). A clear additional advantage of this animal model is its utility in examining individual differences in resilience and susceptibility to chronic stress across multiple molecular and behavioral endpoints. In a population of mice exposed to 10 consecutive days of social defeat, a subset of resilient animals never develop the marked social withdrawal symptoms of their similarly stressed counterparts, which are termed “susceptible.” The interesting part of this study, which adds more validity to the social defeat model, is the demonstration that within this susceptible population, some mice respond to the antidepressant-like effects of imipramine or ketamine (responders) while others do not respond (nonresponders). In this population of responders and nonresponders, Bagot *et al.* (6) conducted transcriptome sequencing in four limbic regions associated with depression in humans, namely the prefrontal cortex, nucleus accumbens, amygdala, and hippocampus. Notably, susceptible mice were treated with the antidepressants imipramine and ketamine in parallel, which results in a rich experimental

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design allowing for the complex investigations of the response to each antidepressant drug within several key limbic structures and allowing a direct comparison between classical and novel antidepressant agents. Overall, the data from this study pointed to the prefrontal cortex as a key structure associated with treatment response to both antidepressants, despite unique region-specific effects of ketamine and imipramine on gene regulation.

In particular, although the amygdala was the site of greatest transcriptional regulation, the prefrontal cortex emerged as a central point of convergence when analyzing region-specific response signatures for each antidepressant agent. Indeed, while both ketamine and imipramine exerted global transcriptional profiles in responders characterized by proresilient and antisusceptible expression patterns, structure-level analyses revealed the highest overlap between ketamine and imipramine responders in the prefrontal cortex when compared with other regions. In other words, the action of both antidepressant drugs to trigger proresilience and reverse prosusceptibility gene expression programs was most similar in the prefrontal cortex. Despite the limited number of antidepressants analyzed in this study, this emphasizes the central role played by this region in antidepressant response across different drug classes and highlights its value as an effective target in the development of therapeutic alternatives for a wide range of individuals.

Beyond such similarities, however, ketamine and imipramine regulated the expression of distinct sets of genes in a structure-specific manner. By taking advantage of the distinction between responders and nonresponders, comparison of these two subpopulations allowed for the identification of similarities and specificities in the transcriptomic signature of antidepressant response following each drug. These analyses thus revealed major roles played by the hippocampus in ketamine response, and the amygdala in imipramine response, whereas ketamine and imipramine responses were the most similar in the prefrontal cortex and nucleus accumbens. Beyond the wealth of new information that these data bring to help better understand the overall molecular bases of antidepressant effects, the identification of drug-specific regulations at a multistructure level can prove highly valuable in understanding their specific contributions at the phenotypic level. For instance, identification of molecular substrates of treatment response unique to ketamine, when compared with imipramine, could provide key insight into the mechanistic underpinnings of its comparatively rapid induction of antidepressant effects, therapeutic capabilities in treatment-resistant depressed patients, or reversal of suicidal ideation. As a result, the brain structures and genes specific to ketamine response represent valuable candidates for understanding response to ketamine but not classical antidepressants in some treatment-resistant patients. In this perspective, the hippocampus emerges as a particularly interesting target for further investigation of ketamine’s advantages over classical antidepressants.

As previously mentioned, a main benefit of this study’s design is the comparison of transcriptomic regulations across four major limbic structures key in controlling depressive-like behaviors and antidepressant response. In addition to providing a wealth of information on the similarities and differences in gene expression changes underlying ketamine and/or imipramine response, these data illustrate the extent of transcriptomic differences between these connected structures. Moreover, these differences were further accentuated following ketamine or imipramine treatment, with each drug triggering a distinct profile of gene

regulations across all four structures. In this context, an appreciable challenge exists in identifying factors stable across structures—especially at the transcriptional level or in a clinical environment—and thus in discovering biomarkers of depressive-like state. Similarly, such specificity in each drug's transcriptomic signature in responders illustrates the difficulty in narrowing down candidates for wide-range therapeutic interventions. However, an alternative approach may rise from another interesting finding from this study. Indeed, nonresponders to either drug exhibited changes in gene expression when compared with saline-treated susceptible mice. In addition to suggesting that nonresponse is an active process, this study thus indicates that the nonresponse to either ketamine or imipramine shares substantial similarities between drugs and across structures. As a result, while the response to either drug is drug and structure specific, the nonresponse emerges as a more general process, at least at the transcriptional level. If such observation is further confirmed at the functional level, this would suggest that preventing the nonresponse to antidepressant treatment may represent a suitable approach in a wide range of individuals and thus open an interesting therapeutic strategy.

Finally, one question that remained unanswered by this study is whether these molecular signatures reported in responders and nonresponders would be similar in female subjects. In fact, because depression is more common in women, it is imperative that better animal models are developed to examine susceptibility/resilience and response to antidepressants in female subjects. Some of our recent work has clearly showed that chronic stress effects and response to antidepressants, and their underlying mechanisms, can be very different between male and female rodents (9,10).

It is important to note that this large set of data represents a unique online resource for any future studies interested in examining the role of some of the identified differentially expressed genes in stress susceptibility, resilience, and response to antidepressants across several key limbic structures. This rich set of data will thus likely one day help in developing novel antidepressant treatments capable of reversing some of the molecular adaptations occurring in a wide range of depressed patients, including nonresponders.

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