Exploring Mechanisms of Depression-Related Behavior and Rapid Antidepressant Action

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Major Depressive Disorder is a serious mental disorder with a profound disease burden, particularly in the United States. Intriguingly, this disease is almost twice as prevalent in females compared to males. Presently, antidepressant treatment for patients with Major Depressive Disorder requires chronic use and first-line treatment is often ineffective. The neurotrophic hypothesis of depression suggests that a) neurotrophins, in particular brain-derived neurotrophic factor, are necessary for maintaining normal mood states and that b) increases in neurotrophin signaling mediate therapeutic effects of clinical antidepressants. In the laboratory, we have explored aspects of the neurotrophic hypothesis of depression and made progress toward understanding the role of brain-derived neurotrophic factor in depression-related animal models as well as its role in the cellular mechanisms underlying antidepressant efficacy. First, we examined whether loss of brain-derived neurotrophic factor in forebrain neurons impacted susceptibility to chronic stress, an animal model of depression, in a gender-specific manner. Next we examined the contribution of dorsal raphe nucleus brain-derived neurotrophic factor signaling on traditional antidepressant efficacy. Finally, we uncovered a novel role for brain-derived neurotrophic factor in mediating effects of rapid antidepressant efficacy. In the course of my studies, we have found that brain-derived neurotrophic factor expression may be more important for protecting females from negative behavioral effects of chronic stress; that brain-derived neurotrophic factor receptor activation in dorsal raphe is essential for traditional antidepressant efficacy; and finally that brain-derived neurotrophic factor is required for the action of novel rapid antidepressant ketamine.