Jump-starting natural resilience reverses stress susceptibility

Novel therapy for treating depression

By Allyson Friedman

Major depressive disorder (MDD) is a severe mental disorder that affects more than 121 million people worldwide, according to the World Health Organization (1, 2). Despite the prevalence of this pathological syndrome, the most effective treatment currently for MDD is a combination of a limited variety of monoamine-based antidepressant medications and psychotherapy. Twenty percent of people with MDD are not helped by existing therapies (3–5), which have been targeting the same serotonergic and noradrenergic systems for over 60 years (6). Most antidepressant treatments have multiple side effects and require weeks to take effect (7). Unfortunately, during this lag period, up to the onset of activation, there is considerable morbidity and a high risk of suicide (8, 9). Thus there is an imperative need for the development of naturally acting antidepressants. A possible reason for the ineffectual treatment of MDD so far has been the incomplete understanding of the nature of depression. Most work in the field, to date, has focused on the passive pathological mechanisms that contribute to the pathogenesis of depression. In contrast, my work focuses on understanding why some individuals are psychophysically normal in response to stress (i.e., resilient to depression), while others succumb to depression (10–14). The majority of the population successfully employs active coping skills in response to stress, such as optimism, rationalization, wishful thinking, relaxation, and humor, which are linked to the function of the mesolimbic reward neural circuitry (15). Thus, current work has only recently begun to understand the neurobiological basis for these psychosocial coping skills (10, 14, 15).

Maintenance of healthy mental function is known to be closely associated with the dopaminergic pathways, specifically from the dopamine (DA) neurons of the ventral tegmental area (VTA) in the reward circuitry. Thus, I explored this circuit for novel therapeutic targets. My studies utilized the well-established social defeat stress mouse model of depression. An increase in the firing rate and bursting events was found in the VTA DA neurons of the brain reward circuitry in susceptible mice, but not in the resilient subgroup (16, 17). Our work further showed that this hyperactivity was causally linked to the susceptible phenotype (18, 19). Because therapeutic efficacy is typically achieved by reversing pathogenic mechanisms, we first utilized optogenetics to demonstrate that inhibition of VTA hyperactivity reversed the susceptible phenotype (18). My work demonstrates that underlying the VTA dopamine neurons’ hyperactivity of depressed (susceptible) mice was an up-regulation of a hyperpolarization-activated current ($I_h$), a key current in the up-regulation of the firing activity (20, 21). Surprisingly, despite resilient mice exhibiting a stable normal firing of these neurons, I found that resilient mice had an even larger $I_h$. This increase in excitatory current was observed in parallel with increased inhibitory potassium channel currents. My research over the past 3 years has demonstrated that resilient animals homeostatically maintain healthy DA neuron activity through a compensatory up-regulation of potassium channels in response to excess hyperactivity. I demonstrated that experimentally enhancing the firing-increasing $I_h$ or optogenetically increasing the hyperactivity of VTA dopamine neurons in susceptible mice, completely reversed depression-related behaviors, an antidepressant effect achieved through resilience-like homeostatic plasticity via an up-regulation of potassium currents. These potassium currents are sufficient to reduce the stress-induced hyperactivity and reduce the pathogenic firing (22). Utilizing a combination of transgenic mice, viral-mediated gene transfer, optogenetics, and electrophysiology, the research exploring this phenomenon was recently published in Science.

My work introduces a conceptually novel therapeutic strategy for treating depression. Instead of dampening the neuron firing found with stress-induced depression, I demonstrated for the first time that further activating these neurons opens a new avenue to mimic and promote natural resilience. This counterintuitive finding introduces a new approach for therapeutic treatment. If a drug could enhance coping and resilience by pushing depressed (or susceptible) individuals past the tipping point, it might have fewer side effects and work as a more naturally acting antidepressant.

REFERENCES

1. WHO Initiative on Depression in Public Health (World Health Organization, 2009).

Runner up: Allyson Friedman

Allyson Friedman received her undergraduate degree from Barnard College at Columbia University and her Ph.D. from Mount Sinai School of Medicine. Dr. Friedman is currently a postdoctoral fellow at Mount Sinai where she is conducting research on the ionic and neural circuit mechanisms of susceptibility and resilience to major depressive disorder to identify novel targets for treatment.
**Novel therapeutic strategy.** Further increasing $I_h$ in susceptible animals or excessive activation of already hyperactive dopamine neurons subsequently induced a homeostatic compensatory up-regulation of $K^+$ channel-mediated currents and established a more stable neuronal status, the same phenomenon observed in natural resilient mice.
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