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From Mice to Men: Can Ketamine Enhance Resilience to Stress?

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The rapid antidepressant properties of intravenous ketamine have ignited high hopes from researchers, clinicians, and patients alike. While bottom-up patient demand has led some clinicians to offer repeated ketamine infusions directly to patients, academic commentators have warned against premature clinical adoption (1), at times likening the field's enthusiasm to the misguided use of stimulants or opiates to induce short-term depression relief. The rapidity of ketamine's antidepressant onset (2-hours post-infusion) is impressive, but effects dissipate almost as rapidly (3-7 days). While the therapeutic benefit far outlasts the drug's half-life, it is nevertheless too brief to be clinically impactful. Repeated infusions extend the effect, but raise concerns regarding safety (e.g., neurocognitive and psychotomimetic side effects), abuse liability, and feasibility. Thus, the future of ketamine research is to identify new treatment strategies—e.g., synergistic treatment combinations, pharmacological alternatives, and novel clinical applications—that will produce more enduring and clinically impactful forms of relief.

In this issue of *Biological Psychiatry*, Brachman and colleagues (2) suggest a potential paradigm shift in the way that ketamine (and other pharmaceutical agents) might be used clinically: as a primary preventative agent. In a carefully designed series of experiments, the authors report that a single infusion of ketamine buffers against depressive-like symptoms following stress. A 'social defeat' paradigm was used, consisting of two weeks of repeated exposures to a particularly nasty (large and aggressive) mouse. Mice injected with 30mg/kg of ketamine 1-week prior to stress exhibited less immobility in the forced swim test (an indicator of decreased 'behavioral despair') and less behavioral avoidance of the aggressor mouse, when compared to their saline-treated counterparts after stress. This basic pattern of findings generalized to two additional forms of stress: learned helplessness (consisting of two weeks of inescapable shocks) and chronic corticosteroid administration (but only when an anesthetic, 90mg/kg dose was given). However, the effects also showed noteworthy boundaries: they were dose-specific; did not generalize to anxiety-like behavior; and were specific to prevention—when stress was given first, followed by ketamine injection, no effect on depressive-like behaviors was found. Finally, stress resilience was not observed as reliably when 3-weeks of fluoxetine were administered (and then withdrawn) prior to stress. Of particular import from a clinical point of view, effects on resilience persisted post-injection to the maximum length of time tested (4-weeks post-injection), hinting at a

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potentially more durable effect of ketamine in depression prophylaxis than has been observed for depression reduction.

The idea of using ketamine as a means of enhancing resilience to stress—thereby preventing new cases of stress-responsive psychiatric conditions, like depression—is compelling. Preventing depression is likely to be easier and more cost-effective than addressing it retroactively, due to a broad range of factors, from depression's cumulative biological burden on the brain and body, to practical difficulties engaging patients in treatment once they're depressed, to the simple fact that it would seem preferable to forestall human suffering entirely than to simply abbreviate it. However, the road to clinical translation of basic research findings is often fraught with pitfalls, due to imperfect mapping across species. One disparity between Brachman et al's findings and the clinical literature stands out: the authors report that ketamine did *not* affect depressive-like behavior in their mouse models when administered following stress. This stands in clear contrast to the clinical literature on ketamine, in which stressors precipitating depressive episodes are presumed to have occurred in the past, while ketamine nevertheless mitigates symptoms. Posttraumatic stress disorder, which by definition involves previous exposure to stress, has also been reported to respond acutely to ketamine, further suggesting that humans react to post-stressor ketamine differently from Brachman's mice. As the authors suggest, the dosing required to induce prophylactic vs. antidepressant effects may be distinct. Dosing may therefore be a key factor in determining the breadth of ketamine's potential as a buffer against stress, particularly if both pre-stress (e.g., pre-war zone deployment) and acute post-stress (e.g., in the emergency room following an accident) administrations are envisioned.

The psychiatry research of the here and now is equal parts 'Does it work?' and 'If yes, how?' Two intriguing clues are provided regarding the mechanisms of ketamine's effects on stress resilience—which, as the authors note, could be quite distinct from ketamine's antidepressant mechanisms. First, mice who received prophylactic ketamine showed less stress-induced HPA axis dysfunction; by contrast, neuroplasticity-related mechanisms, implicated repeatedly in ketamine's antidepressant effects (3), were absent in the prophylactic model. Second, intriguingly, there was evidence for social/behavioral, 'inter-mouse' mechanisms. During the second week of repeated attacks from the aggressor, ketamine-treated—mice were less likely to stay still compared to saline-treated mice. Akin to the human literature suggesting an unrealistically optimistic outlook can enhance resilience (under some circumstances, at least (4)), this pattern seems to beg for a cognitive interpretation, suggesting ketamine-treated mice approached the aggressor wearing rose-colored (mouse-sized) glasses. More fascinating still, the aggressor mouse showed behavioral changes in response to the ketamine-treated mice—exhibiting longer latency to initial attack. This is reminiscent of human literature suggesting individuals who are prone to stress-related disorders are also prone to stressful experiences themselves, and play an active role in generating the very stressors (e.g., interpersonal conflicts) that then seal their fate (5). In other words, resilience might mean not only that you respond to stress more adaptively, but that you actively construct a world in which the most stressful possibilities within any given context are less likely to occur.

Looking beyond the current set of findings, the authors describe their work as a first attempt to extend resilience enhancement to the domain of clinic-ready pharmaceuticals. Indeed, similar stress-buffering effects were observed for fluoxetine in a subset of analyses (specifically, after chronic cortisol administration), hinting at a wider scope of prophylactic interventions. It's therefore useful to consider the broader field of interventions with known antidepressant properties (pharmacological and otherwise), and their pros and cons in pursuit of depression prophylaxis. While the rapidity of ketamine's antidepressant onset may be particularly useful for managing acute psychiatric emergencies (e.g., suicidality) or preparing for highly imminent stress exposures, many real-world contexts may permit a more leisurely time course (e.g., troops gearing up for deployment). Both maintenance of conventional antidepressants (6) and prior exposure to specific behavioral skills (e.g., cognitive therapy, mindfulness, computer-based attentional training (6-8)) lowers the risk of relapse among remitted depressed patients; whether these treatments can buffer against *de novo* psychiatric disorders is a worthy question. A rich literature exists in humans documenting the psychosocial factors that correlate with resilience (e.g., optimism, faith or 'moral compass,' social support; (4,9)), and behavioral approaches to enhancing resilience through these factors have shown promising, if modest, results (e.g., 10). The challenge in this area, as in psychiatry on the whole, is to reach the largest number of individuals in need, at the lowest cost, burden, and risk. Whether ketamine becomes a useful addition to the clinical prevention toolkit will ultimately depend on the cost-benefit math.

Finally, the term resilience requires that adversity will occur; no adversity, no resilience. Another challenge for clinical translation will be to identify appropriate conditions that should trigger administration of resilience-enhancing treatments. At one extreme, given the ubiquity of stress, a 'universal prevention' approach could be imagined following a vaccine-like model, where the entire population would be inoculated in the hopes of preventing all cases of stress-related psychiatric dysfunction. This approach may strike many readers as improbable for a multitude of reasons, including the difficulties inherent in disseminating psychiatric treatments to even those at clearest need, the absence of an anticipated 'herd immunity' boost (as exists for infectious diseases), and, perhaps, a societal tendency to view a certain degree of emotional struggle as a meaningful and sometimes valuable component of life. Notably, even Brachman's mouse strain (129S6/SvEvTac) was selected to be *vulnerable* to social defeat, making findings most applicable to 'selective' rather than 'universal' prevention. So, what combinations of person-level characteristics and environmental conditions should be taken into account when prescribing resiliency-enhancing treatment? Should offspring of depressed parents receive such a vaccine as they enter sensitive developmental periods, like adolescence or the transition to college? Children with an abuse history, who now face bullying? Soldiers with sub-threshold symptoms preparing for war-zone deployment? Under what conditions would you sign up for such a vaccine, or encourage loved ones to?

Ideally, the basic science initiated in this line of research will be pursued in a manner that helps reveal rational algorithms to inform this type of clinical decision-making. Perhaps specific forms of stress, in combination with specific genetic, experiential, and/or biological preconditions, will implicate one mechanistic target for resilience enhancement, while different conditions will require a different intervention—or none at all. Such 'precision

medicine' questions have proven quite challenging to address in the messy land of humans, but elegant experimental designs in animals have tremendous potential. When practical clinical considerations inform the questions asked in basic research (as they clearly did in this case), and the answers obtained guide clinical research and, ultimately, clinical application, we will have arrived at the promised land of translational medicine.

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