STRESS AND RESILIENCE

Ketamine and the female brain

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Ketamine is an NMDA-receptor antagonist that has been used as a general anesthetic since the 1970s. More recently, low doses have been used off-label as a potential treatment for depression and other stress-related disorders, though it has yet to complete clinical trials and be approved by the FDA for this use. Basic and preclinical researchers who are interested in how ketamine affects the brain have been studying the drug in animal models like rats, but those studies have tended to be biased towards males. In 2016, Steven Maier and Linda Watkins' lab at the University of Colorado Boulder published a study in the *Journal of Neuroscience* demonstrating that prophylactic use of ketamine could buffer the effects of a stressful situation in Sprague Dawley rats. But, only male rats were tested. PhD student Sam Dolzani was aware of the gender gap in the literature—and that stress-related disorders tend to affect women more than men—so he decided to test ketamine again in the missing gender.

Like the lab's earlier paper, the current study started with behavioral testing, but this time they had an improved technique to follow what was also happening in the brain. Dolzani used a tagging strategy recently developed by researchers at the University of Colorado and MIT known as RAM, or robust activity marker, that can label activated cells at different time points. Cells in the prelimbic cortex that were activated by ketamine were labeled at the beginning of the experiment; one week later, cells that were activated by a stressful situation were labeled with a different marker. The researchers could then quantify the neurons that were labeled by both ketamine and stress "to see if the same cells were involved at both time points," Dolzani explains.

As in males, low-dose prophylactic ketamine seemed protective against uncontrolled stress. Following a tail shock, females who received ketamine were more active during a social exploration test, a behavioral measure of anxiety. Looking more closely at the brain, it appears that ketamine activates a circuit in the brain involved with resilience and resistance to stress. When the team shut off that circuit by inhibiting it with DREADDS—designer receptors exclusively activated by designer drugs—ketamine showed no positive buffering effects.

Males will still need to be tested with the double-labeling technique to see if the same pathways and effects are at play, and Dolzani notes that future research should also consider other behavioral outcome measures. Nevertheless, the results underscore the importance of not forgetting females.

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