Archival Report

Biological Psychiatry

Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior

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ABSTRACT

BACKGROUND: Stress exposure is one of the greatest risk factors for psychiatric illnesses like major depressive disorder and posttraumatic stress disorder. However, not all individuals exposed to stress develop affective disorders. Stress resilience, the ability to experience stress without developing persistent psychopathology, varies from individual to individual. Enhancing stress resilience in at-risk populations could potentially protect against stress-induced psychiatric disorders. Despite this fact, no resilience-enhancing pharmaceuticals have been identified.

METHODS: Using a chronic social defeat (SD) stress model, learned helplessness (LH), and a chronic corticosterone (CORT) model in mice, we tested if ketamine could protect against depressive-like behavior. Mice were administered a single dose of saline or ketamine and then 1 week later were subjected to 2 weeks of SD, LH training, or 3 weeks of CORT.

RESULTS: SD robustly and reliably induced depressive-like behavior in control mice. Mice treated with prophylactic ketamine were protected against the deleterious effects of SD in the forced swim test and in the dominant interaction test. We confirmed these effects in LH and the CORT model. In the LH model, latency to escape was increased following training, and this effect was prevented by ketamine. In the CORT model, a single dose of ketamine blocked stress-induced behavior in the forced swim test, novelty suppressed feeding paradigm, and the sucrose splash test.

CONCLUSIONS: These data show that ketamine can induce persistent stress resilience and, therefore, may be useful in protecting against stress-induced disorders.

Keywords: Depression, Ketamine, Mice, PTSD, Stress, Stress resilience

http://dx.doi.org/10.1016/j.biopsych.2015.04.022

Stress commonly precipitates psychiatric illness, particularly in vulnerable populations. For example, one in five soldiers returns from combat with posttraumatic stress disorder or combat-associated major depressive disorder (MDD) (1). Perhaps more surprising is that many soldiers do not develop psychopathology. While there has been extensive research on factors promoting susceptibility to psychiatric illnesses, few studies have examined what makes individuals resistant or stress resilient. Until recently, the sparse research on stress resilience has been predicated on the assumption that it is a passive property—more or less the absence of the risk factors that make individuals susceptible to stress-induced pathology (2). Recent work in animal models suggests that stress resilience is mediated through active processes and often distinct, parallel mechanisms to those of susceptibility (3–5).

The idea that increasing stress resilience could protect against the development of psychiatric disorders is appealing, but treatments to increase resilience are still in their infancy. Current interventions fall predominantly on the behavioral side, with psychotherapy and exercise being the best available tools to increase resilience (6–8). Rodent studies further support a role for exercise and enriched environment in stress resilience (9–11). Beyond behavioral manipulations in mice, researchers have successfully increased resilience biochemically through viral and transgenic overexpression methods (12), optogenetic activation (4), and chronic blockade of stress hormones (13,14). However, none of these interventions translates to the clinic. Most promisingly, we have identified the immune system as a novel target for enhancing resilience. Our recent work has shown that manipulating leukocytes is sufficient to increase stress resilience (15) and Hodes *et al.* (16) have shown a similar effect by modulating cytokines. Though hopefully these discoveries will lead to therapeutic interventions in humans, they are not yet clinic ready.

Antidepressants are typically used to treat existing depressive symptoms, but chronic antidepressant treatment also protects against subsequent depressive episodes (17–21). Maintenance treatment in MDD patients is often referred to as prophylaxis against the development of additional depressive episodes (22). Whether this prophylactic effect against symptomatic episodes in disordered individuals extrapolates out to preventing de novo psychiatric disorders remains to be tested.

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 ISSN: 0006-3223

Ketamine has been shown to have antidepressant effects as rapidly as 2 hours following a single injection in patients with MDD (23). Whereas classic antidepressants require ongoing daily administration to maintain therapeutic efficacy, ketamine has the benefit of being administered as a single dose (23,24). Because ketamine has a window of therapeutic efficacy far beyond its half-life of a few hours (23–25), it is an excellent candidate for a plausible approach to pharmacologically increasing stress resilience.

Therefore, we first utilized social defeat (SD) to examine whether ketamine could increase stress resilience and, thereby protect against de novo induction of psychopathology. We hypothesized that ketamine would confer stress resiliency to mice if administered before stress. We chose to perform SD in 129S6/SvEvTac mice, which robustly and reliably develop a depressive-like phenotype following SD (26). Mice were administered either saline or a single subanesthetic injection of ketamine, and 1 week later, SD was administered to half of the mice. We found that a single injection of ketamine induced robust stress resilience that persisted for at least 3 weeks postinjection. Moreover, we confirmed our effects in two additional models in which depressive/anxious behavior is induced by chronic elevation of glucocorticoids in C57BL/6NTac mice (27) or by repeated, unescapable shocks (learned helplessness [LH]) (28–30). Again, a single subanesthetic dose of ketamine, administered 4 weeks before behavioral assessment, decreased immobility in the forced swim test (FST) and protected against depressive-like behavior in the novelty suppressed feeding (NSF) paradigm and the sucrose splash test (ST). In the LH model, the latency to escape a shock increases with LH training and this effect was prevented by prophylactic ketamine. These findings demonstrate that the protective effect of ketamine extends at least 4 weeks postinjection. To our knowledge, this is the first study to examine the potential of psychopharmaceuticals to provide long-term prophylactic protection against the induction of stress-related disorders.

METHODS AND MATERIALS

Mice

Male 129S6/SvEvTac mice were purchased from Taconic (Hudson, New York). CD-1 mice were purchased from Charles River Laboratories (Wilmington, Massachusetts) at 8 to 10 weeks of age and housed individually until the start of SD. The procedures described herein were conducted in accordance with the National Institutes of Health regulations and approved by the Institutional Animal Care and Use Committees of Columbia University and the New York State Psychiatric Institute.

Male C57BL/6NTac mice were purchased from Taconic Farms (Lille Skensved, Denmark) at 8 weeks of age and were housed five per cage before the start of corticosterone (CORT) treatment. All testing was conducted in compliance with the laboratory animal care guidelines and with protocols approved by the Institutional Animal Care and Use Committee (European Directive, 2010/63/EU for the protection of laboratory animals, permissions # 92-256B, authorization ethical committee CEEA n°26 2012_098).

All mice were housed in a 12-hour (600–1800) light-dark colony room at 22°C. Food and water were provided ad libitum. Behavioral testing was performed during the light phase.

RESULTS

Ketamine Administration Before SD Protects Against the Induction of Depressive-like Behavior

Mice were administered a single injection of saline or ketamine (30 mg kg^{-1}) (Figure 1A). One week later, mice either remained group housed (Ctrl) or underwent SD. After 2 weeks of SD, mice were weighed (Supplemental Figure S2A), and behavior was assessed.

Classically, immobility in the FST has been interpreted as an index of hopelessness or a negative mood (31). Rodents given acute or chronic antidepressants exhibit decreased immobility (32). Here, on day 2 of the FST, there was an overall effect of SD on immobility time. Ctrl-saline (Sal) and Ctrl-ketamine (K) mice displayed equal levels of immobility time (Figure 1B). In SD mice, ketamine (SD-K) significantly decreased immobility time when compared with saline (SD-Sal) (Figure 1C, D). These data indicate that ketamine increases resilience to behavioral despair as measured by the FST.

Dominant interaction is a robust way of testing the induction of depressive-like behavior by SD (10) (Figure 1E). As expected, SD-Sal mice spent significantly more time investigating an empty enclosure quadrant than Ctrl-Sal mice (Figure 1F). Ctrl (Sal or K) mice spent an equivalent amount of time investigating the empty enclosure quadrant. SD-K mice exhibited significantly less time investigating the empty enclosure quadrant when compared with SD-Sal mice. Similarly, SD-K mice exhibited a significantly increased willingness to interact with the CD-1 when compared with SD-Sal mice (Figure 1G). There was an overall effect of SD and of ketamine on decreasing the distance traveled, but the interaction was not significant (Figure 1H).

To determine if this exploration deficit extended to neutral environments, open field exploration was investigated in an arena scented with female urine (Supplemental Figure S3). We did not detect any differences in the empty quadrant or the urine quadrant between Ctrl and SD mice. Furthermore, to determine if social avoidance generalized to other mice, we also assessed social interaction with a novel mouse (Supplemental Figure S4). We did not find an effect of SD or ketamine on social interaction. In summary, these data suggest that SD decreases exploration and willingness to interact with a CD-1 aggressor and that prior ketamine administration protects against this deleterious effect of SD on social behavior.

An Injection of Ketamine Before SD Does Not Impact Anxiety-like Behavior or Contextual Fear Memory

We next examined the effects of ketamine on anxiety-like behavior and cognitive tests. In the NSF paradigm, we found no significant effect of SD or ketamine on the latency to feed (Figure 2A). In fact, all groups showed similar latencies