A Single Subanesthetic Dose of Ketamine Relieves Depression-like Behaviors Induced by Neuropathic Pain in Rats

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ABSTRACT

Background: Chronic pain is associated with depression. In rodents, pain is often assessed by sensory hypersensitivity, which does not sufficiently measure affective responses. Low-dose ketamine has been used to treat both pain and depression, but it is not clear whether ketamine can relieve depression associated with chronic pain and whether this antidepressant effect depends on its antinociceptive properties.

Methods: The authors examined whether the spared nerve injury model of neuropathic pain induces depressive behavior in rats, using sucrose preference test and forced swim test, and tested whether a subanesthetic dose of ketamine treats spared nerve injury-induced depression.

Results: Spared nerve injury-treated rats, compared with control rats, showed decreased sucrose preference (0.719 ± 0.068 (mean ± SEM) vs. 0.946 ± 0.010) and enhanced immobility in the forced swim test (107.3 ± 14.6s vs. 56.2 ± 12.5s). Further, sham-operated rats demonstrated depressive behaviors in the acute postoperative period (0.790 ± 0.062 on postoperative day 2). A single subanesthetic dose of ketamine (10 mg/kg) did not alter spared nerve injury-induced hypersensitivity; however, it treated spared nerve injury-associated depression-like behaviors (0.896 ± 0.020 for ketamine vs. 0.663 ± 0.080 for control rats 1 day after administration; 0.858 ± 0.017 for ketamine vs. 0.683 ± 0.077 for control rats 5 days after administration).

Conclusions: Chronic neuropathic pain leads to depression-like behaviors. The postoperative period also confers vulnerability to depression, possibly due to acute pain. Sucrose preference test and forced swim test may be used to complement sensory tests for assessment of pain in animal models.

What We Already Know about This Topic

• Ketamine reduces depressive symptoms in patients in small reports, but whether this effect is independent of pain relief in patients with chronic pain has not been addressed.

What This Article Tells Us That Is New

• In rats with neuropathic hypersensitivity, low-dose ketamine reduced behavioral measures of depression without altering hypersensitivity.
Depression affects 30–100% of patients with chronic pain and is likely underestimated in postoperative pain. Depression leads to additional emotional and cognitive deficits, and understanding the relationship between pain and depression will help to tailor treatments. There is evidence that depression alters the threshold of pain, although few studies examined whether depression is an integral affective component of the pain experience.

In rodents, pain is often assessed by sensory hypersensitivity, measured by stereotyped behaviors such as limb withdrawal. Hypersensitivity is an important sensory feature, but does not reveal cognitive and emotional responses to pain, which can be assessed by Morris water maze, elevated plus maze, and open field tests.

In rodents, depression can be measured by forced swim test (FST) and sucrose preference test (SPT). FST, a test for behavioral despair, was used to examine depression in the spinal nerve ligation model of neuropathic pain. Whereas Kontinen et al. reported no changes in the FST performance in rats 14 days after surgery, Suzuki et al. found rats displayed depressive traits 15 days postoperatively. SPT measures anhedonia, a key feature of depression. SPT, however, was rarely used in pain studies.

Ketamine has both analgesic and antidepressant properties and is ideally suited to treat pain-induced depression. Ketamine antagonizes N-methyl-D-aspartic acid receptors in spinal dorsal horn neurons to decrease central sensitization, providing descending monoaminergic inhibition, and blocks Na⁺ channels and μ-opioid receptors in peripheral fibers. Ketamine is metabolized within 1 h and is useful as a short-acting analgesic. Although ketamine may block central sensitization to mediate long-acting analgesia, this remains to be proven in clinical practices. In contrast, clinical studies have shown that ketamine provides enduring antidepressant effects.

Several proposed mechanisms explain the antidepressant properties of ketamine: increased presynaptic glutamate release and up-regulation of postsynaptic machinery in the prefrontal cortex, and increased brain derived neurotrophic factor expression in the hippocampus. Thus, whereas short-lived analgesic properties of ketamine are mediated at peripheral and spinal levels, its antidepressant activities involve frontal and limbic structures and are long-lasting. Clinically, depression can be treated at a lower dose than pain.

Similarly, in rats, less than 10 mg/kg ketamine provides antidepressant effects but more than 25 mg/kg is needed for analgesia. Therefore, determining whether ketamine can treat depression-like behaviors at a dose (less than 10 mg/kg) that does not treat sensory hypersensitivity in rats may provide a distinction between sensory and depressive components of pain.

We examined the spared nerve injury (SNI) model in rats. Using a combination of SPT and FST, we found that rats exhibited depression-like behaviors immediately after surgery. Whereas depression-like behaviors induced by sham operation were reversible, depression induced by SNI surgery was chronic. These results suggest that depression may be a key feature of postoperative and chronic pain in rats; hence we favor the routine use of SPT and FST in pain assessments. Moreover, a single subanesthetic dose of ketamine produced rapid and enduring antidepressant effects in rats with chronic pain, without decreasing sensory hypersensitivity, suggesting that depressive symptoms of pain can be modulated independently of sensory symptoms.

Materials and Methods

Animals

All procedures in this study were approved by the New York University School of Medicine Institutional Animal Care and Use Committee as consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (publication number 85–23) to ensure minimal animal use and discomfort. Male Sprague-Dawley rats were purchased from Taconic Farms, Albany, NY and kept in the New York University Langone Medical Center’s Central Animal Facility, with controlled humidity, room temperature, and 12-h (6:30 AM to 6:30 PM) light-dark cycle. Food and water were available ad libitum. Animals arrived at the animal facility at 250–300 g and were given approximately 14 days to adjust to the new environment before the onset of any experiments.

SNI Surgery

The SNI surgery has been previously described in detail. Briefly, under isoflurane anesthesia (1.5–2%), the skin on the lateral surface of the right thigh of the rat was incised and a section made through the biceps femoris muscle to expose three branches of the sciatic nerve: sural, common peroneal, and tibial nerves. The common peroneal and tibial nerves were tied with nonabsorbent 5.0 silk sutures at the point of trifurcation. The nerves were then cut distal to the knot, and approximately 3–5 mm of the distal ends were removed. In sham surgeries (control), these nerves were dissected but not cut. Muscle and skin layers were then sutured close in distinct layers. Naïve rats underwent no surgery.

Drugs

Ketamine hydrochloride (Ketaset) was purchased from Fort Dodge Animal Health, Fort Dodge, IA. Ketamine was diluted in saline to a concentration of 1–50 mg/ml (depending on the final dose of ketamine). For the ketamine experiments, rats that underwent SNI surgery were assigned to two subgroups, one receiving ketamine injections and the other saline (control) injections. The rats received 1, 3, 10, 20, or 50 mg/kg ketamine injected intraperitoneally in the ketamine group (0.3–0.5 ml), whereas a similar volume of saline was injected intraperitoneally to the control group. Injections were given at least 14 days after SNI surgeries and were followed by behavioral tests.
Animal Behavioral Tests

Mechanical Allodynia Testing. A traditional Dixon up-down method with von Frey filaments was used to measure mechanical allodynia. In brief, rats were individually placed into Plexiglass chambers over a mesh table and acclimated for 20 min before the onset of examination. Beginning with 2.55 g, von Frey filaments in a set with logarithmically incremental stiffness (0.45, 0.75, 1.20, 2.55, 4.40, 6.10, 10.50, 15.10 g) were applied to the lateral third of right paws (in the distribution of the sural nerve) of animals before and up to 56 days after SNI or sham surgery and to rats that underwent no surgery but similar handling (naïve group). In addition, the tests were done on the left (uninjured) paws of the SNI animals. The 50% withdrawal threshold was calculated as described previously. For ketamine experiments, mechanical allodynia tests were done 1 h or 1 day after ketamine (or saline) injection, and observers were blinded to the test conditions (ketamine vs. saline treatments).

Cold Allodynia Testing. Animals were individually placed into Plexiglass chambers as above and acclimated for 20 min. A drop of acetone was applied to the lateral plantar surface of the paws (in the distribution of the sural nerve). As previously described, the following scoring system was applied. 0: no visible response or startle response lasting less than 0.5 s; 1: paw withdrawal lasting less than 5 s; 2: withdrawal lasting 5–10 s, with or without licking of the paws; 3: prolonged repetitive withdrawal lasting more than 10 s. Acetone was applied five times to each paw, and an average score was calculated. Cold allodynia tests were typically done after mechanical alldynia tests on the same day, and observers were blinded to the test conditions (ketamine vs. saline treatments).

Sucrose Preference Test. Animals were trained approximately 2 h each day for 7–10 days to drink from two identical bottles, one containing 1% sucrose solution and the other water. In order to avoid side preference, the bottles were placed on alternating sides every day. Before the SNI surgery, baseline preference for sucrose was established. During each test, two bottles (1% sucrose solution vs. water) were presented to each animal for 30 min, and then the bottles were switched to the opposite side, and the test continued for an additional 30 min. At the end of each test, sucrose preference was calculated as volume of sucrose consumed divided by total liquid consumption for each rat. Based on their baseline preferences, animals were equitatively assigned to the naïve, sham surgery, or SNI surgery group. After undergoing surgery, sucrose preference was then tested on postoperative day 2, 7, 14, and 56 for the SNI and sham surgery groups and 2, 7, and 14 for the naïve group. For ketamine experiments, all animals underwent SNI surgery, and animals were assigned to either the ketamine or saline group. Due to the variability of baseline presurgical sucrose preference, animals were assigned to treatment and control groups with the goal of ensuring that the average baseline preference for each group was approximately the same before each experiment. At 14 days after the SNI surgery, ketamine or saline was injected into each animal, and sucrose preference was then tested 1 and 5 days after the injection. Observers were blinded to the test conditions (ketamine vs. saline treatments).

Statistics

The results of behavioral experiments were given as mean ± SEM. For mechanical allodynia, a two-way ANOVA with post hoc multiple pairwise comparison Bonferroni correction tests was used to compare the 50% withdrawal threshold of the right and left legs of the SNI animals, and right legs of sham-operated and naïve animals. Cold alldynia was analyzed using the Kruskal-Wallis test with post hoc Dunn multiple pairwise comparison tests at each time point. A one-way ANOVA with post hoc multiple pairwise comparison Tukey post hoc tests was used to analyze mechanical alldynia of SNI-treated animals that received higher doses of ketamine (20 or 50 mg/kg) or saline, and a Kruskal-Wallis test with post hoc Dunn multiple pairwise comparison tests was used to analyze the cold alldynia data. Weight gain was analyzed using the Kruskal-Wallis test with post hoc Dunn multiple pairwise comparison tests.
using a two-way ANOVA with post hoc multiple pairwise comparison Bonferroni correction tests. For the sucrose preference test, a two-way ANOVA with post hoc Bonferroni correction tests was used to compare the preference at different time points of the SNI, sham-operated, and naïve groups, and to compare the preference at different time points of rats injected with ketamine or saline. In the dose-response experiment, a two-way ANOVA with post hoc Bonferroni correction tests was used to compare sucrose preference for different doses of ketamine (1, 3, 10, and 20 mg/kg) versus saline control. For the FST, a unpaired two-tailed Student t test was used to compare the performances of sham-operated and SNI groups as well as to compare the performances of ketamine and saline groups. For corticosterone levels and total fluid consumption during the SPT, a one-way ANOVA was conducted. For all tests, a P value less than 0.05 was considered statistically significant. All data were analyzed using GraphPad Prism Version 4 software (GraphPad, La Jolla, CA). We did not perform a power analysis a priori for our experiments. The numbers of subjects used in our experiments were based on our experience with these behavioral tests and in agreement with standard literature. Same or similar numbers of subjects were used in control and test conditions. Thus, if the test condition provided statistical significance but the control did not, we would conclude that the control condition resulted in nonmeaningful findings.

Results

SNI Produced Long-lasting Sensory Hypersensitivity without Changes in the Stress Level or Overall Well-being of the Animals

We studied the SNI model for neuropathic pain. Comparable with previous reports,43 we found that SNI surgery produced significant mechanical and cold hypersensitivity in the (spared) sural nerve distribution acutely, on postoperative day 1, and these effects persisted for up to 2 months (fig. 1A, 1B). In contrast, rats that underwent sham surgery or no surgical manipulation (naïve rats) did not demonstrate any sensory hypersensitivity in the spared nerve distribution. In addition, we observed no hypersensitivity in the uninjured paw of an animal after the SNI surgery. SNI results in neuropathy, which may produce chronic stress to complicate behavioral tests. To rule out this possibility, we used weight gain as a measure for the overall health and well-being of rats and found no difference among SNI-treated rats, naïve (non-operated) rats or sham-operated rats (fig. 1C). Furthermore, we measured levels of the stress hormone corticosterone of rats 14 days after surgery and found no differences among rats in the SNI, sham-operated, and naïve groups (fig. 1D).

SNI Produced Depressive Behaviors

Next, we applied standard tests of depression to rats in chronic pain. The first test we used was the FST. Increased time of immobility (instead of swimming) in a water tank is considered a measurement of behavioral despair. We performed our tests 14 days after the surgery—a standard time for the development of chronic neuropathic pain—and found that compared with sham-operated rats, rats after treatment for SNI developed significantly increased time of immobility (fig. 2A). We confirmed this expression of depressive behavior with the SPT, which assesses anhedonia, measured by the preference of sucrose solution to water. At baseline, sham-operated and SNI-operated rats demonstrated approximately more than 90% preference for sucrose (1%) solution over water. However, 14 days after surgery,
SNI-operated rats demonstrated significantly decreased preference for sucrose compared with sham-operated rats, and this difference lasted up to 2 months (fig. 2B), concurrent with the time course of chronic sensory hypersensitivity demonstrated by SNI animals (fig. 1A and B). Next, we turned our attention to the early postoperative period (postoperative days 1 through 14). Because we were concerned about postoperative incisional pain associated with sham operations, we added an additional control group—naïve rats, who underwent no surgeries. Rats in both SNI and sham surgery groups developed significantly decreased preference for sucrose in the immediate postoperative period (fig. 2C, postoperative day 2), compared with the naïve group. This decrease in sucrose preference was transient in the sham surgery group, lasting less than 7 days. In contrast, the decrease in the SNI group was stable. To ensure that neuropathy resulting from SNI did not interfere with drinking behaviors, we measured the total fluid consumption and did not find any differences among the three groups of animals (fig. 2D).

**Low-dose (10 mg/kg) Ketamine Provided Long-lasting Antidepressant Effects**

If SNI causes depressive behaviors, then an antidepressant should be able to treat these behaviors. We applied a single dose of ketamine (10 mg/kg) known to treat depression versus saline (control) intraperitoneally to animals that had undergone SNI surgery 14 days previously. One day after drug administration, we tested the sucrose preference for these animals. Although animals that received saline injection remained anhedonic, animals that received ketamine injections demonstrated a return to baseline presurgical sucrose preference (fig. 3A). Although ketamine improved sucrose preference, it did not affect total volume of fluid consumption (fig. 3B). We repeated these tests 5 days after the injection to determine whether the antidepressant effect of ketamine was enduring. We found animals that received ket-
amine 5 days previously continued to demonstrate improvements in anhedonia (fig. 3A). We next used the FST to confirm the antidepressant effects of ketamine in animals after SNI surgeries. One day after ketamine administration, animals with neuropathy showed a significant improvement in their immobility score, compared with those animals that received saline injections (fig. 4). In fact, the immobility score for SNI-operated animals after ketamine treatment was comparable with that of sham-operated animals.

**Low-dose (Less Than 50 mg/kg) Ketamine Did Not Modify Sensory Hypersensitivity in Animals after SNI Surgery**

Because ketamine also carries antinociceptive properties, we next asked whether the antidepressant effect of ketamine that we found at this dose (10 mg/kg) caused improvements in sensory hypersensitivity. We administered a single dose of ketamine (10 mg/kg) intraperitoneally to animals that had undergone SNI surgery 14 days previously. Because the half-life of ketamine is less than 1 h and its analgesic effects are short acting, we tested its analgesic effects 1 h and 1 day after injection. At this dose, we did not observe any changes in mechanical or cold hypersensitivity compared with saline (control) either 1 h after the injection, or 1 day after injection (fig. 5A through D). To further verify the lack of long-acting (more than 1 h) antinociceptive effects of ketamine, we also tested sensory hypersensitivities at two higher doses, 20 mg/kg and 50 mg/kg, 1 day after administration (we did not perform these tests 1 h after drug administration because sedative side effects of ketamine interfered with behavior tests). At these doses, we still did not observe any changes in mechanical or cold hypersensitivity compared with saline (fig. 5E and F). This lack of long-lasting analgesia contrasted with the enduring antidepressant effects that we observed up to 5 days after ketamine injection (fig. 3A). These results suggested that the antidepressant effects of ketamine we observed are independent of the antinociceptive effects of ketamine at low subanesthetic doses.

**Dose-Response Relationship for the Antidepressant Activity of Ketamine**

Next we sought to determine the dosage required to establish antidepressant effects for ketamine. We applied a series of doses – 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg – and compared the antidepressant effects of these doses of ketamine with saline control using the SPT. As shown in figure 6, at 10 or 20 mg/kg, antidepressant effects were fully established statistically \((P < 0.01\) for 10 mg/kg, \(P < 0.05\) for 20 mg/kg).
the underlying mechanisms remain un-
surgery and persisted up to 2 months. Surprisingly, sham-
Persensitivity as indices for pain, we found that both depres-
sensory hypersensitivity. Third, a single subanesthetic
treatment for neuropathy-induced depression without affecting sen-
sence was found at 10 and 20 mg/kg ketamine. **P < 0.01 for
post hoc Bonferroni correction tests. 1 mg/kg group: n = 4;
ketamine did not treat neuropathy but reduced immobility
symptoms of depression and may form the link
al.
Dose-response relationship for the antidepressant
effects of ketamine. A series of escalating doses of ketamine
(1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg) were applied to
rats 14 days after spared nerve injury (SNI) and are compared
with saline control. The sucrose preference test was per-
formed 1 day after drug administration. Statistical signifi-
cance was found at 10 and 20 mg/kg ketamine. **P < 0.05 for
20 mg/kg, two-way ANOVA with
Discussion
Depression and pain are important comorbidities. In the
current study, we used a rat neuropathic pain (SNI) model to
test if pain causes depression-like behaviors. Our study had
three key findings. First, both SNI and sham surgeries
rapidly induced depression-like behaviors. Second, de-
pression induced by SNI was chronic and concurrent with
sensory hypersensitivity. Third, a single subanesthetic
dose of ketamine provided quick and enduring treatment
for neuropathy-induced depression without affecting sen-
sory hypersensitivity.
Using behavioral despair (in FST) and anhedonia (in
SPT) as indices for depression and mechanical and cold hy-
persensitivity as indices for pain, we found that both depres-
sion-like behaviors and pain quickly developed after SNI
surgery and persisted up to 2 months. Surprisingly, sham-
operated rats also developed reversible postoperative depres-
ion. Although postoperative depression has been described
clinically, the underlying mechanisms remain unknown.
One possible cause is pain. In our model, it was
difficult to test incisional pain after sham surgery using sen-
sory tests, but the time course of depression that we observed
(less than 7 days after surgery) correlated with the time course
of acute postoperative pain in other models. Possible causes of depression include surgical stress and inflam-
mation, but these were unlikely causes in our experiments as
weight gain and stress hormone levels were unchanged
among the test groups. In the future, it will be instructive to
test depression in a postoperative pain model such as the paw
incision model. At the same time, our results provided an
explanation for studies by Kontinen et al. and Suzuki et al.,
where affective changes such as anxiety and depression
were not detected until 14 days after the spinal nerve ligation
surgery. Thus, in these studies, the control group–sham-operated rats may have also experienced affective changes in
the initial postoperative period, and the difference in FST
performance between the test group (spinal nerve ligation) and the control group (sham) may have been obscured as a
result.
In rodent studies, pain has traditionally been tested by
sensory hypersensitivity. Pain, however, also has cognitive
and affective components. Previous studies on the depres-
sion-like response to pain have focused on the FST, but the FST requires some motor competence. We observed that
rats in the SNI group used their noninjured legs more often
than the injured legs during the FST. This deviation did not
affect our conclusions because we measured time of immo-
Biol, which did not require motor coordination; and ket-
amine did not treat neuropathy but reduced immobility
associated with the SNI surgery. Increased immobility in the
FST could be caused by spontaneous pain, which may make
rats less likely to move, independent of depression. We can-
note rule out this possibility, but we think this interpretation
is unlikely. First, for spontaneous pain to increase the time of
immobility in the FST, all SNI-treated rats would have had
to experience spontaneous pain within the 5-min interval of
the FST (fig. 2). Second, ketamine at high doses (50 mg/kg)
did not provide relief for evoked pain (fig. 5), suggesting that
at lower doses (10 mg/kg) it may not provide relief for spont-
aneous pain either. In contrast, ketamine (10 mg/kg) im-
proved immobility in the FST (fig. 4). Therefore, we believe
the increased immobility observed in the FST was unlikely
caused by spontaneous pain, but rather, reflected depression-
like behaviors. To further confirm this observation, we used
SPT, another commonly used test for depression in rodents.
Compared with FST, SPT has minimal requirements for
motor competence, and findings are less likely confounded
by motor deficits or spontaneous pain. Combining the SPT
with the FST, we are the first group to show that depressive
behaviors develop rapidly after surgery and persist in a chronic
fashion with neuropathic pain. We argue that depressive behav-
iors are a key feature of pain in rats, and hence SPT and FST
should be used routinely in pain assessments.
The molecular mechanisms for how pain causes de-
pression are not well studied. However, pain has been
shown to cause altered synaptic connectivity at the pre-
frontal cortex and hippocampus, as well as altered
signaling from the ventral tegmental area. These biochemical changes have been known to trigger
negative symptoms of depression and may form the link
between pain and depression.
An alternative explanation for our data is that surgeries
induced depression and pain independently. Neuropathy
from SNI may create chronic stress that causes depression.
However, this is unlikely in our study. First, we did not
observe any weight differences—-a good measure for general
well-being—among SNI-treated, sham-treated and naive rats.
Second, we did not detect differences in levels of the stress hormone corticosterone among the three groups. A number of studies have examined stress levels in neuropathic pain models and found no association between pain and chronic stress.13,22 Another possible cause of depression from SNI is neuroinflammation. However, in the sham surgery, nerves were not dissected and we would not expect any neuroinflammation, but sham surgery still caused reversible depression. In our study of neuropathic pain, it was difficult to test the hypothesis that relieving pain would treat depression, because drugs used to treat neuropathic pain (opioids, antidepressants, or anticonvulsants) can alter performances in the FST and the SPT independently. In the future, it will be interesting to test depression using a reversible pain model, such as the acute postoperative pain or the inflammatory pain model.

Ketamine treats both depression and pain. Clinically, ketamine has not consistently demonstrated long-lasting analgesic effects at low doses. Rodent studies have shown more than 25 mg/kg is necessary for antinociception.40–42 The duration of antinociception is also variable, but most often limited to within 24 h.27,41 It is possible that ketamine relieved spontaneous pain at low doses, but higher doses are required to treat evoked pain (tested by mechanical and cold hypersensitivities). However, even at higher doses of ketamine (20 and 50 mg/kg), there was no relief of evoked pain 24 h after administration (fig. 5). Thus, ketamine did not likely provide long-lasting analgesia for evoked or spontaneous pain at subanesthetic doses. In contrast, both clinical and animal studies have shown that ketamine provides antidepressant effects that last from days to weeks.32–34 At 10 mg/kg ketamine is known to treat depression38 without causing psychomotor side effects.27,41 We observed statistically significant relief of depression beginning 1 day after ketamine administration and lasting 5 days. Therefore, at this dose ketamine appeared to illustrate a distinction between the sensory and affective responses to pain. This result has threefold significance. First, it further validates the use of FST and SPT in pain studies. A concern with higher order behavioral tests is that their results may be confounded by spontaneous or movement-associated pain. Ketamine reduced immobility without changing hypersensitivity, implying that immobility in our study was not likely caused by the sensation of painful movement. Rather, it more likely reflected behavioral despair, an index for depression. The same is true for the SPT. The second significance of this finding is that the effective dosage (10 mg/kg) and time course (at least 5 days) of ketamine therapy in our model was highly compatible with other models of depression.32,38,61 This suggests that the underlying mechanism of ketamine’s antidepressant function may be conserved among different models of depression. Whereas analgesic properties of ketamine are mediated at spinal and peripheral level,26–28 its antidepressant effects have been shown to be mediated at cortical and limbic areas.37–38 Our results argue that ketamine likely ameliorates pain-induced depression at the supraspinal level. Third, our result shows that we can selectively target the depressive symptoms of pain without altering the sensory component. This concept has high clinical relevance, especially when the sensory component of pain is difficult to treat, such as the case with complex regional pain syndrome or phantom limb pain. In clinical studies, ketamine has been shown to improve mood in patients with phantom limb pain long after its analgesia effects have worn off.62 Mood improvements are critical for physical rehabilitation during the postoperative period and for functional recovery among patients with chronic pain.46,63–65 Ketamine may have an important role in this area of pain treatment, given its quick onset of action and enduring activity. Our preclinical data, therefore, advocate further investigation into the clinical use of ketamine as an effective and specific antidepressant in pain patients.

In conclusion, we found that pain rapidly and stably induces depression, but pain-induced depression can be treated by ketamine at low doses without treating the sensory input. These data argue that standard tests of depression such as the SPT and the FST should be applied to the battery of pain tests in rat studies. They also suggest that the affective component of pain can be selectively targeted successfully. Clinically, our results encourage careful evaluation and aggressive treatment of depression in both acute and chronic pain patients; they also show that low-dose ketamine may have a unique role in treating the depressive symptoms of neuropathic pain.

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