Accepted version
Published in Progress in Neuro-Psychopharmacology & Biological Psychiatry
Progress in Neuro-Psychopharmacology & Biological Psychiatry 8: 109898, 2020
10.1016/j.pnpbp.2020.109898

Ketamine induces rapid and sustained antidepressant-like effects in chronic pain induced depression: role of MAPK signaling pathway.

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Abstract

Chronic pain produces psychologic distress, which often leads to mood disorders such as depression. Co-existing chronic pain and depression pose a serious socio-economic burden and result in disability affecting millions individuals, which urges the development of treatment strategies targeting this comorbidity. Ketamine, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, is shown to be efficient in treating both pain and depression-related symptoms. However, the molecular characteristics of its role in chronic pain-induced depression remain largely unexplored. Hence, we studied the behavioral and molecular effects of a single systemic administration of ketamine (15 mg/kg, i.p.) on mechanical hypersensitivity and depressive-like consequences of chronic neuropathic pain. We showed that ketamine transiently alleviated mechanical hypersensitivity (lasting < 24h), while its antidepressant effect was observed even 72 hours after administration. In addition, ketamine normalized the upregulated expression of the mitogen activated protein kinase (MAPK) phosphatase 1 (MKP-1) and the downregulated phosphorylation of extracellular signal-regulated kinase (pERK) in the anterior cingulate cortex (ACC) of mice displaying neuropathic pain-induced depressive-like behaviors. This effect of ketamine on the MKP-1 was first detected 30 minutes after the ketamine administration and persisted until 72h. Altogether, these findings provide insights into the behavioral and molecular changes associated with single ketamine administration in the comorbidity of chronic pain and depression.

Keywords: Ketamine; Neuropathic pain-induced depression; Comorbidity; Anterior cingulate cortex; MKP-1; pERK

Abbreviations: ACC, anterior cingulate cortex; ATF1, transcription factor 1; CREB, cyclic AMP (adenosine monophosphate) response element binding protein; ERK, extracellular signal regulated kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen activated protein kinase; MKP-1, MAPK phosphatase-1; NMDA, N-Methyl-d-Aspartate; pERK, phosphorylated ERK; GABA, Gamma aminobutyric acid.

1. Introduction

Chronic pain and depression are detrimental conditions affecting an increasing number of people around the world (Bair et al., 2003; Rayner et al., 2016). Moreover, the co-existence of these conditions represents a serious socio-economic burden and results in a more pronounced disability and a poorer prognosis than either condition alone (Arnow et al., 2006; Gallagher and Verma, 1999). Preclinical data suggests that the comorbid relationship of chronic pain and depressive-like behaviors can be modeled in murine models (Humo et al., 2019; Yalcin et al., 2014a), which allows studying molecular characteristics and treatment strategies in more depth.

Ketamine is a versatile pharmacological agent described in 1965 (Domino et al., 1965) and extensively used in clinical practice since 1970 (Aroni et al., 2009). It primarily acts as a noncompetitive antagonist of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptors (Bergman, 1999). Although initially used as a dissociative anesthetic, ketamine has been later shown efficient in treating both depression and pain (Abdallah et al., 2015; Persson, 2013).

However, while there is widespread evidence of ketamine use for the individual treatment of chronic pain and depression in humans (Aan Het Rot et al., 2012; Hocking and Cousins, 2003), evidence for its beneficial use in the comorbidity of these two conditions is highly limited (Bigman et al., 2017; Weber et al., 2018). Moreover, despite the increasing number of evidence accumulated over the past several decades about the antidepressant and antinociceptive activity of ketamine (Cohen et al., 2018; Sleigh et al., 2014; Zanos and Gould, 2018a, b), the underlying mechanism of ketamine action in the chronic pain induced depression has not yet been elucidated.

We have recently shown that neuropathic pain-induced depressive like behaviors in mice are associated with the upregulation of the mitogen activated protein kinase (MAPK) phosphatase-1 (MKP-1) in the anterior cingulate cortex (ACC) (Barthas et al., 2017), a brain structure implicated in both pain- and mood- related processing (Barthas et al., 2015). MKP-1 dephosphorylates both threonine and tyrosine residues of MAPKs thereby acting as an important negative regulator of the extracellular signal-regulated kinase (ERK) signaling cascades (Jeffrey et al., 2007). The relation between MKP-1 and ERK is bidirectional as ERK signaling can also regulate transcription factors such as the cyclic- adenosine monophosphate (cAMP) response element binding protein (CREB) and transcription factor 1 (ATF1) found on the *Mkp-1* promoter region (Rastogi et al., 2013). The present study aimed to determine if neuropathic pain-induced depressive-like behaviors are associated with a disruption of this

feedback loop and whether ketamine exerts its activity by targeting different members of the MAPK signaling pathway.

Specifically, the present study evaluated the effect of systemic ketamine administration on the mechanical hypersensitivity and depressive-like consequences of neuropathic pain as well as its effect on the MAPK signaling pathway. Our main results showed that a single intraperitoneal (i.p.) injection of ketamine (15 mg/kg) results in rapid reduction of depressive-like behaviors lasting several days, while only transiently alleviating mechanical hypersensitivity. This ketamine-mediated phenotype was accompanied by a decrease in MKP-1, starting from 30 minutes (min) and lasting at least until 72 hours (h), and by an increase in phosphorylated ERK (pERK) in the ACC of neuropathic animals. The current findings shed light on the molecular alterations accompanying ketamine administration in the comorbidity of chronic pain and depression.

2. Materials and Methods

2.1. Animals

110 adult male C57BL/6J mice (Charles River, L'Arbresle, France) were used. The mice were 8 weeks old at the beginning of the experiments, housed 4 per cage and kept under a 12h light/dark cycle (lights on: 7 p.m and off: 7 a.m) with food/water availability ad libitum. Results were obtained from a total of four independent cohorts of animals, wherein two were used for behavioral testing and two were used for western blot analyses. Protocols were approved by the University of Strasbourg ethics committee and performed according to animal care and use guidelines of the European Community Council Directive (EU 2010/63).

2.2 Neuropathic pain model and nociception assessment

Animals were anaesthetized with a combination of zoletil (25 mg/kg tiletamine and 25 mg/kg zolazepam) and xylazine (10mg/kg) (Centravet, Taden, France) i.p. before neuropathy was induced by unilateral implantation of a 2mm polyethylene tube (cuff) around the main branch of the right sciatic nerve (Yalcin et al., 2014b). Control (sham) mice received the same surgery without placing the cuff. The mechanical threshold was assessed before surgery (baseline) and on a weekly basis in the postoperative period with the von Frey test. During each session, the animals were individually habituated (10 min) in transparent, bottomless plastic boxes which were placed on a mesh platform. Next, filaments of different pressure (0.4 - 8.0 g; Bioseb, Chaville, France) were applied to the ventral surface of each hindpaw in an ascending fashion. A positive response for a given pressure was recorded when 3 out of 5

applications resulted in withdrawal or licking of the stimulated hindpaw. The mechanical sensitivity threshold was characterized as a response to 2 consecutive filaments.

2.3. Pharmacological agents

Ketamine hydrochloride (Yliopiston Apteekki, Helsinki, Finland) was dissolved in 0.9% sodium chloride (NaCl) to a 3 mg/ml concentration and injected 0.10 - 0.15 ml i.p., depending on the weight of the animal, to achieve a 15 mg/kg of ketamine dose per animal. Control animals received single i.p. injections of 0.9% NaCl.

2.4. Behavioral tests

The presence of anxiodepressive-like behaviors was assessed during the 8 week of post neuropathy induction. All the tests were performed during the animals' active phase (dark cycle), under red light and as previously described (Yalcin et al., 2011). The experimental design is detailed in Fig. 1A and Fig. 2A.

2.4.1. Novelty-suppressed feeding test

Food deprived (24 h) mice were placed in the corner of an open plastic box (40 cm x 40 cm x 30 cm) containing 2 cm of sawdust and a food pellet in the center. The latency to first contact and start eating the pellet was recorded within a time frame of 5 min after being placed in the box. The test measures the animal's motivation to approach the open space of the center of the arena where the food is located.

2.4.2. Splash test

This test involved spraying a 20% sucrose solution onto the dorsal coat and recording of animal´s total grooming activity over the next 5 min. A reduced grooming rate indicates a loss of motivation for self-hygiene, parallel to human apathy.

2.4.3. Forced swimming test

Each animal was slowly lowered into a glass cylinder (17.5 cm height x 12.5 cm diameter) with 12 cm of water (24°C). Two minutes after, the immobility time, which involved floating on the surface without active swimming movements, was recorded over the next 4 minutes. Due to the stressful circumstances, this test was always performed last. The test measures the animal's helplessness-like behavior.

2.5. Tissue collection and protein analysis

For the molecular analyses, animals were sacrificed 30 min or 72 h after ketamine injection by cervical dislocation and the ACC was dissected and stored at -80°C. Next, protein

extraction, followed by Western blot was performed. Protein extraction was started by mechanical dissociation of the tissues in lysis buffer (20 mM Tris pH 7.5, 150 mM NaCl, 15% EDTA, 10% glycerol, 1% NP40) and centrifugation of the lysate (15,000 g/4°C/10 min). Next, the supernatant was recuperated (100 µl) and a fraction of it used to determine its concentration with a protein assay (Quick Start Bradford, Bio-Rad, Munich, Germany) and spectrophotometry (Mitrhras LB940, Berthold Technologies). After adjusting the concentration of each sample to 1 µg/µl with lysis and Laemmli buffers, SDS-PAGE gel electrophoresis was done by separating 15 µl of the denatured proteins on 8% polyacrylamide gels and electroblotting them onto a polyvinylidene fluoride (PVDF) membrane (Millipore). Finally, the membrane was incubated over night at 4°C in the primary antibody (anti-MKP-1, ab195261 lot GR239206-8 rabbit monoclonal, 1:60000; Abcam or pERK Phospho-p44/42 MAPK (Erk1/2) ref 9101 lot 28 rabbbit monoclonal; 1:600 Cell signaling), washed with TBST, and then incubated in the secondary antibody for 1h under agitation (AP370P Milipore lot 2899737; goat anti-rabbit; 1:10000 or 1:7500, respectively). Imaging was performed with the enhanced chemiluminescence detection system (ECL Amersham) using the Amersham Imager 680 system. The relative protein expression was calculated with the densitometry tool of Adobe Photoshop CS3 software.

2.6. Statistical analysis

All graphical results are expressed as mean ± SEM (standard error of mean). Statistical analyses were performed with STATISTICA 7.1 (Statsoft, Tulsa, Oklahoma) by using multifactor analysis of variance (ANOVA), with independent (Two-way ANOVA) or repeated measures and Duncan post hoc analyses. The significance level was set at $p \leq 0.05$. For detailed information see Supplementary table S1.

3. Results

3.1. Single ketamine administration transiently relieves neuropathy-induced mechanical hypersensitivity

Prior to the sciatic nerve cuffing surgery, we evaluated the mechanical threshold for nociceptive sensitivity using the von Frey filaments and organized the groups in such a way that their baseline sensitivity would be equal (Fig. 1B and C). After neuropathy induction, both sham operated and neuropathic mice were divided into a group which later received ketamine and one which received saline, resulting in a total of 4 different groups. Before ketamine administration, cuff-implanted animals consistently showed mechanical

hypersensitivity in the ipsilateral paw, which lasted more than eight weeks after the surgery (Fig. 1C; $F_{(4, 100)} = 6.86$, $p \leq 0.001$). At 8 weeks, we first established the time-response curve of single dose of ketamine (15 mg/kg, i.p.) on mechanical sensitivity. We observed that ketamine alleviated the decreased mechanical threshold observed in neuropathic animals 3 h after the administration but this effect was no longer present at 24 h post-treatment (Fig. 1D and D', $p \leq 0.001$). This rapid but transitory allodynia relief was not observed in neither sham nor neuropathic animals administered with saline (Fig. 1D and D'). Since the motor performance is an important cofounder for behavioural tests, we assessed the locomotor activity of animals 8 weeks after the surgery. The results confirmed our previous observation that the cuff surgery does not affect spontaneous activity (Fig. 1E, (Barthas et al., 2017; Barthas et al., 2015; Sellmeijer et al., 2018; Yalcin et al., 2011)) and also demonstrated for the first time that ketamine does not alter the locomotor activity at 1h after its administration, the time point at which we performed our first behavioral test (Fig. 1E).

3.2. Single ketamine administration ameliorates depressive-like behaviors in neuropathic mice

Compared to the control animals which received a sham surgery, peripheral nerve injury resulted in depressive behaviors 8 weeks after the surgery, as displayed by an increased latency to feed in the NSF test (Fig. 2B; $p \leq 0.05$), a decreased grooming duration in the Splash test (Fig. 2C; $p \leq 0.05$) and an increased immobility in the FST (Fig. 2D; $p \leq 0.001$). While the anti-allodynic effect was transient, a single injection of a subanesthetic dose of ketamine was sufficient to reduce neuropathy-induced depressive-like behaviors for a prolonged period of time (Fig. 2B-E). Specifically, the neuropathic animals showed a decrease in depression-related behaviors 1h after ketamine administration in the NSF test (Fig. 2B; $p \leq 0.01$), 24 h after in the Splash test (Fig. 2C; $p \leq 0.05$) and 72 h after in the FST (Fig. 2D; $p \leq 0.05$). However, the antidepressant-like effect of ketamine ceased 2 weeks after the treatment since we observed no differences between saline and ketamine treated cuff animals (Fig. 2E; $p > 0.05$).

3.3. Single ketamine administration restores the disrupted MAPK signaling pathway

The level of the MKP-1 in the ACC was evaluated 30 min and 72 h after the ketamine administration using two different batches. Western blot analysis showed that MKP-1 protein level was increased in the ACC of saline injected animals displaying neuropathic pain-induced anxiodepressive-like behaviors both at 30 min (Fig. 3A; $F_{(1, 19)} = 4.08$, $p \leq 0.05$; post

hoc: sham saline < NP saline, $p \leq 0.01$) and 72 h (Fig. 3C; $F_{(1, 18)} = 8.69$, $p \leq 0.01$; post hoc: sham saline < NP saline, $p \leq 0.01$). This increase was diminished 30 minutes and 72 hours after single ketamine administration (Fig. 3A; $p \leq 0.01$; Fig. 3C; $p \leq 0.01$). Similarly, neuropathic animals displayed a decreased p-ERK protein level in the ACC (Fig. 3B; $F_{(1, 20)} = 0.42$, $p \leq 0.05$; post hoc: sham saline > NP saline, $p \leq 0.01$) which was restored 30 min after single ketamine administration (Fig. 3B; NP saline < NP ketamine, $p \leq 0.05$).

4. Discussion

By using a mouse model of the comorbidity of neuropathic pain and depression, the present study demonstrated that systemic administration of a single sub-anesthetic dose of ketamine (15 mg/kg) is sufficient to: i) transiently alleviate mechanical hypersensitivity; ii) decrease depressive-like behaviors induced by chronic pain for up to 72 h; iii) restore the increased MKP-1 and the decreased p-ERK protein levels in the ACC.

Treating chronic pain and depression in an independent manner is challenging, but the comorbidity of these disorders is far more difficult (Bair et al., 2003). Subclasses of classical antidepressant drugs such as tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors and anticonvulsants such as gabapentin and pregabaline (Gilron et al., 2015) remain among the first line treatments for many chronic pain conditions as they have direct analgesic effects. Additionally, other treatments such as topical lidocaine, cannabinoids and opioids are used (Attal et al., 2010; Dworkin et al., 2010). Even with these possibilities, there is still a lack of efficiency, and a considerable amount of patients experiencing side effects (Chou et al., 2015; Finnerup et al., 2010), which poses an urgent need for alternative pain remedies. In the current study, we demonstrated that a single systemic administration of ketamine (15 mg/kg) alleviated mechanical allodynia in nerve injured mice 3 h after the administration, but the hypersensitivity was restored already at 24 h post-injection. This transient anti-nociceptive effect of a single ketamine administration is in accordance with previous results (Koizuka et al., 2005; Qian et al., 1996).

One of the main targets of ketamine are the NMDA receptors which are crucial in the development and maintenance of central sensitization (Petrenko et al., 2003), characterized by an increase in dorsal horn excitability, resulting in hypersensitivity, hyperalgesia and allodynia (Woolf, 2011). Thus, by inhibiting NMDA receptors, ketamine has been shown effective in the alleviation of pain in patients suffering from various conditions, including post-surgical pain (Stubhaug et al., 1997), fibromyalgia (Graven-Nielsen et al., 2000), complex regional pain syndrome (Schwartzman et al., 2009) and neuropathic pain (Jorum et

al., 2003). However, it is necessary to utilize higher cumulative doses, as well as prolonged serial infusions to achieve a longer lasting effect following the treatment (Niesters et al., 2014; Sigtermans et al., 2009). Curiously, a recent study using the same neuropathy model as here showed that a prolonged ketamine treatment (twice a day for 10 days) with the same dose (15 mg/kg i.p.) had different results depending on the time period of the drug administration (Salvat et al., 2018). Indeed, when ketamine was administered before neuropathic pain surgery, progressive recovery of mechanical allodynia was observed until 2 months after the cessation of the treatment. However, starting ketamine administration with a 25-day delay after neuropathy induction produced only partially recovery during the 10-day treatment, and allodynia completely returned 2 weeks post-treatment. These results suggest that ketamine efficiency is not only dependent on the dose and frequency of administration, but also on the temporal progression of chronic pain (i.e. development vs. maintenance phase).

Besides its effect on the somatosensory component of chronic pain, here we showed that a single injection of ketamine at a sub-anesthetic dose is sufficient to relieve neuropathic pain-induced depressive-like behaviors for at least 72 h, well beyond the acute pharmacological effects (elimination t1/2 ~10-15 min). The current study is the first to use a mouse model of comorbid neuropathic pain and depressive-like behaviors to show the antidepressant-like effect of acute ketamine administration, which has previously been shown only in rats (Wang et al., 2011) and in some clinical case studies (Bigman et al., 2017; Weber et al., 2018). These results are also in accordance with previous data from stress-related rodent models of depressive-like behaviors (Autry et al., 2011; Li et al., 2010) and human patients with major depressive disorder (Ballard et al., 2014; Berman et al., 2000; Zarate et al., 2006) showing that ketamine is a rapid-acting, long-lasting antidepressant agent whose therapeutic effects are manifested within hours and sustain for several days. This is in contrast to the generally prescribed, monoaminergic-related drugs which take several weeks or even months to manifest their benefits (Insel and Wang, 2009; Machado-Vieira et al., 2010). Thus, it is of great interest in the field of psychiatric disorders, notably depression, to understand the physiochemical mechanisms behind the fast-acting, long-term antidepressant properties of ketamine (Abdallah et al., 2015; Kavalali and Monteggia, 2015).

We then studied where and how ketamine acts. The transient antinociceptive and prolonged antidepressant effect of acute ketamine administration observed in the current study highlights the distinct sensory and affective responses to chronic pain. The fact that the duration of ketamine's antidepressant benefits surpasses its anti-nociceptive action suggests

that the analgesic properties of ketamine might be mediated at the spinal and peripheral level (Koizuka et al., 2005; Oatway et al., 2003; Sawynok and Reid, 2002), whereas its antidepressant effects require the recruitment of cortical and limbic areas such as the ACC, hippocampus and amygdala (Li et al., 2017; Moghaddam et al., 1997; Niesters et al., 2012). Among these brain structures, the ACC seems to be critical for chronic pain induced depression (Barthas et al., 2017; Barthas et al., 2015) as well as for the antidepressant action of ketamine. For instance, Perrine et al. (Perrine et al., 2014) showed that ketamine administration resulted in an increase of GABA levels in the ACC of rats subjected to chronic unpredictable stress. This is in line with previous studies showing a decreased level of GABA in the ACC of depressed patients (Bhagwagar et al., 2008), as well as an overall depression-associated hyperactivity of the ACC in both rodents (Sellmeijer et al., 2018) and humans (Drevets et al., 2002). Interestingly, it has been recently shown that acute ketamine reduces hyperactivity of ACC neurons induced by chronic pain in rats (Zhou et al., 2018), which might point to a potential mechanism through which it also exerts its antidepressant activity. Accordingly, we performed all the mechanistic studies in the ACC.

Since the activation of NMDA receptors is related to an increase in intracellular MAPKs, including ERK, p38 and the c-Jun N-terminal kinase (JNK) (Crown et al., 2006; Ji et al., 2009; Waxman and Lynch, 2005) and our neuropathic pain induced depression model induces alterations in this pathway in the ACC as well, we decided to focus on the impact of ketamine on the MAPK pathway in the ACC. Our results showed that an acutely administered ketamine attenuates the disrupted MAPK signaling pathway in the ACC of mice displaying neuropathic pain-induced depressive-like behaviors. Specifically, ketamine lowered the elevated ACC MKP-1 protein level in neuropathic mice at 30 min and 72 h after the drug administration, while it had no effect on the expression of MKP-1 in the ACC of control mice. In addition, ketamine restored the decreased p-ERK in the ACC of mice with comorbid neuropathic pain and depressive-like behaviors. These results are supported by recent evidences from pain field suggesting that ketamine's analgesic activity might be partly mediated through the modulation of several members of the MAPK pathways (Choi et al., 2009; Kwon et al., 2014; Mei et al., 2011). Specifically, it was shown that ketamine's analgesic effect is associated with an inhibition of both spinal astrocyte JNK activation (Mei et al., 2011) and the increased expression of p38 and phospho-p38 (Kwon et al., 2014) as well as with a decreased upregulated ERK (Choi et al., 2009) in the spinal cord of rats with neuropathic pain. In accordance with these findings, it has been shown that a single dose of subanesthetic ketamine which recruits the MAPK signaling cascade (Kohtala et al., 2019; Li

et al., 2010) also ameliorates chronic stress-induced deficits in spine number and function (Li et al., 2011), a common characteristic in depression (Banasr et al., 2011). Moreover, Réus et al. (Reus et al., 2014) found that acute blockade of MAPK signaling is sufficient to induce depressive-like behaviors and prevent the antidepressant response to ketamine. Therefore, ketamine might exert its effect by altering the sustained negative regulation of MAPKs through MKP-1, which is thought to contribute to the neuronal atrophy and volume loss in limbic brain areas associated with depression (Sheline et al., 1996; Stockmeier et al., 2004). This has already been suggested as a potential mechanism of other pharmacological agents which alter the MAPK pathway in pain and depression-associated brain regions (Duman and Voleti, 2012). For instance, evidences suggest that antidepressants such as fluoxetine and imipramine might act by restoring the dysregulated expression of MKP-1 and ERK in the hippocampus and ACC (Barthas et al., 2017; Duric et al., 2010; Yasuda et al., 2014).

Besides the ACC, ketamine has been shown to alter the expression of *Mkp-1* in brain regions like the striatum or hippocampus (Ficek et al., 2016). The reason we focused solely on the ACC is the absence of MKP-1 alterations in other brain regions in our mouse model of chronic pain-induced depression, including the hippocampus and the somatosensory cortex (Barthas et al., 2017).

While our results suggest that upregulated MKP-1 contributes to increased dephosphorylation of ERK, which, in turn, fosters the development of depression, the relationship of MKP-1 and ERK does not seem to follow a linear direction, and this pattern of altered expression does not always seem to be the case. In fact, some previous studies show that both chronic stress and neuropathic pain are associated with an increase in ERK activation in the ACC (Kuipers et al., 2003; Wei and Zhuo, 2008), and that this activation contributes to the induction of affective pain, including aversion in response to painful stimuli (Cao et al., 2009; Dai et al., 2011). Additionally, by combining chronic constriction injury and chronic mild stress, Bravo et al. (Bravo et al., 2012) showed that rats with comorbid chronic pain and depressive-like behaviors show a robust increase of ERK in the ACC. Moreover, Yasuda et al. (Yasuda et al., 2014) demonstrated that chronic constriction injury induces an up-regulation of pERK1/2 in the ACC of rats, while treatment with the tricyclic antidepressant imipramine successfully reduced this overexpression. The observed discrepancies might stem from the intricate bi-directional relationship between MKP-1 and ERK, which might be differently regulated depending on the condition and specific cells and networks. Namely, although MKP-1 is the negative regulator of ERK (Boutros et al., 2008; Sun et al., 1993), it has been demonstrated that ERK can induce *mkp-1* gene expression at the

transcriptional level (Brondello et al., 1997), as well as enhance its phosphatase activity (Slack et al., 2001), reflecting its role in a negative feedback control. On the other hand, it is also known that activated ERK can trigger MKP-1 proteolysis via the ubiquitin-proteasome pathway, hence achieving a positive feedback loop by decreasing its phosphatase activity (Lin et al., 2003). These findings suggest that, depending on whether kinase activity needs to be sustained or inhibited, ERK has a dual function in regulating MKP-1 stability, which is achieved through docking to its different domains (Lin and Yang, 2006).

In addition to NMDA receptor antagonism and MAPK inhibition, ketamine produces indirect opioid system activation, demonstrated first in clinical studies (Williams et al., 2019; Williams et al., 2018). Recently Malinow's group showed that ketamine does not act as an opiate, but its effects require both NMDA and opiate receptor signaling, suggesting that interactions between these two neurotransmitter systems are necessary to achieve an antidepressant effect (Klein et al., 2020). Besides its antidepressant effect, the implication of opioid receptors has also been shown in the analgesic effect of ketamine. Indeed, the antagonists of μ- and δ- but not kappa-opioid receptors block ketamine-induced central antinociception (Pacheco Dda et al., 2014).

In conclusion, this study clearly showed that ketamine could serve as alternative treatment for neuropathic pain patients with major depressive disorder as it has a dual effect on both the somatosensory and emotional consequences of chronic pain. While our study shows the sustained effect of ketamine on MAPK pathway, the present study could not directly test the causal link between ketamine-induced changes in MKP-1 and the relief of depressive-like symptoms. Indeed, since the pharmacological blockade or genetic suppression of MPK-1 being sufficient *per se* to suppress or prevent depressive-like behaviors in animal models (Barthas et al., 2017; Duric et al., 2010), the direct testing of the role of MKP-1 downregulation in ketamine action becomes very difficult.

Funding information

This work was supported by the Centre National de la Recherche Scientifique (contract UPR3212), the University of Strasbourg, NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (24736), Fondation pour la Recherche Médicale (FRM FDT201805005527), French National Research Agency (ANR) through the Programme d'Investissement d'Avenir under the contract ANR-17-EURE-0022. This study was also supported by The Scientific and Technological Research Council of Turkey (TUBITAK)

through the 2219 international post-doctoral research fellowship program and the Academy of Finland (grant nro. 276333). We would like to thank Chronobiotron for animal care.

Declaration of Competing Interest: None. The authors declare that they have no conflict of interest. The funding sources had no role in the study design, in the interpretation of data and in the writing of the manuscript.

Ethical Statement

Protocols were approved by the University of Strasbourg ethics committee and performed according to animal care and use guidelines of the European Community Council Directive (EU 2010/63).

Figures

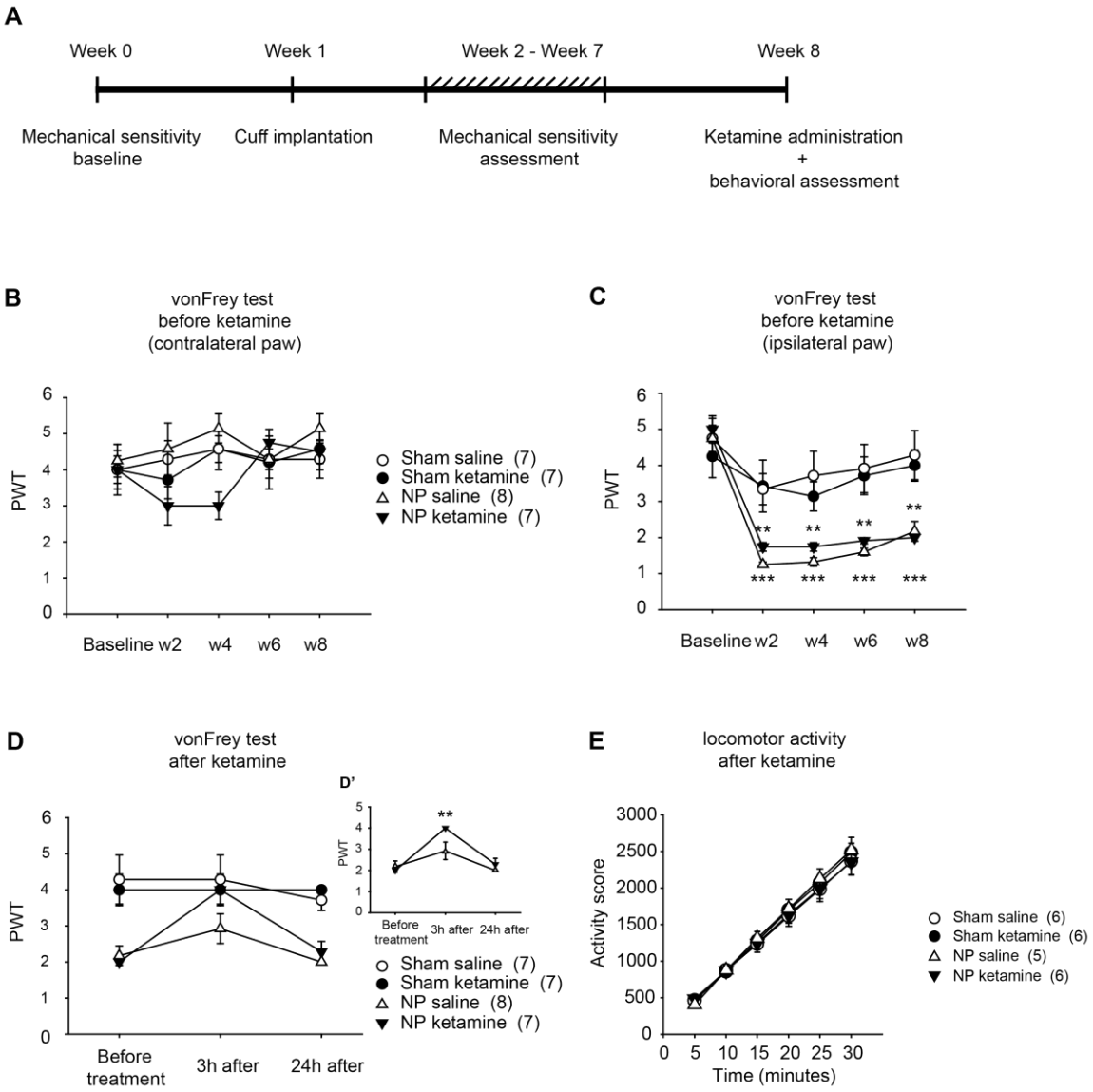

Fig. 1. Antinociceptive effects of single systemic ketamine administration. A) Timeline of surgical and behavioral procedures. B) Pre-ketamine treatment mechanical sensitivity showing no difference in the post-surgery threshold of the contralateral paw of sham and neuropathic (NP) mice as assessed by von Frey test. C) von Frey test results from different time points during the post-surgery period showing a decreased mechanical sensitivity threshold of the ipsilateral paw of NP mice compared to sham-operated controls. D) von Frey test results after single ketamine, showing an increase in the mechanical sensitivity in the ipsilateral paw of NP mice at 3 h (D'), but not 24 h, after administration. E) Neither the peripheral nerve injury nor ketamine treatment affects the spontaneous locomotor activity.

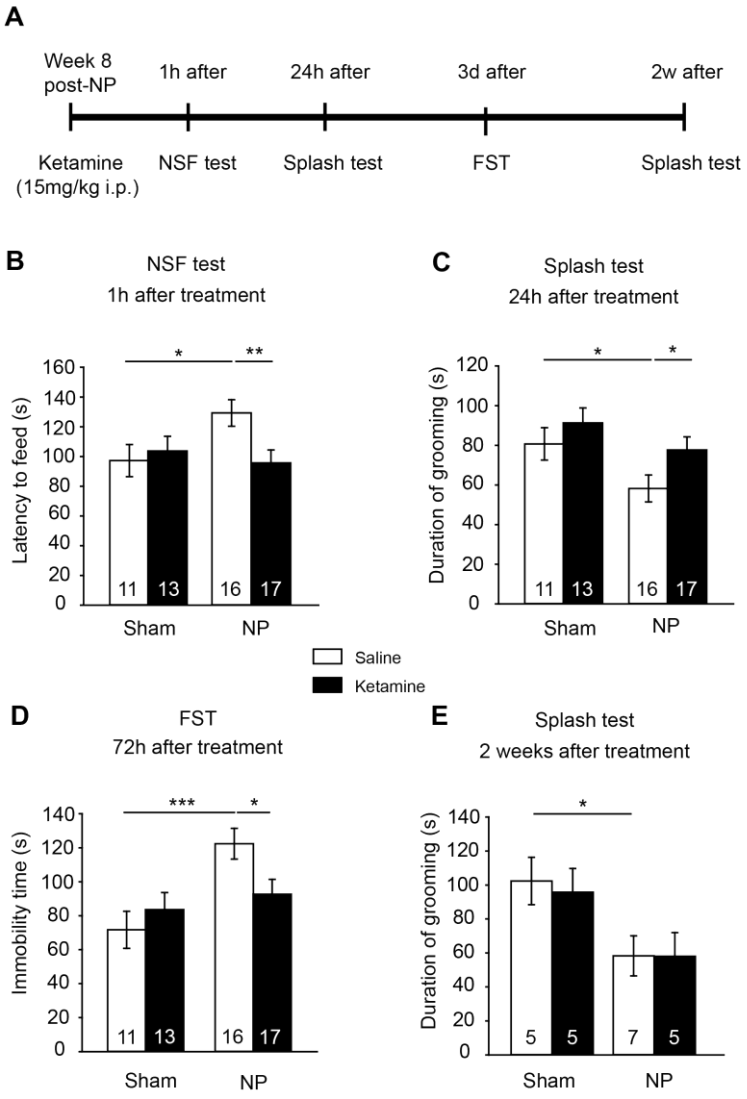

Fig. 2. Antidepressant-like effect of single systemic ketamine administration.

A) Timeline of surgical and behavioral procedures. B) NSF test showing a decrease in the latency to feed of NP mice 1 h after ketamine injection. C) Acute ketamine treatment resulted in an increased grooming duration of NP animals in the splash test 24 h later. D) Ketamine-treated NP mice showed a decrease in immobility time during FST 72 h after administration. E) Two weeks after ketamine injection, there was no difference in the grooming duration in the splash test between treated and non-treated NP mice, suggesting that the antidepressant-like effect of acute ketamine was no longer present. Sample sizes are presented in brackets next to experimental groups.

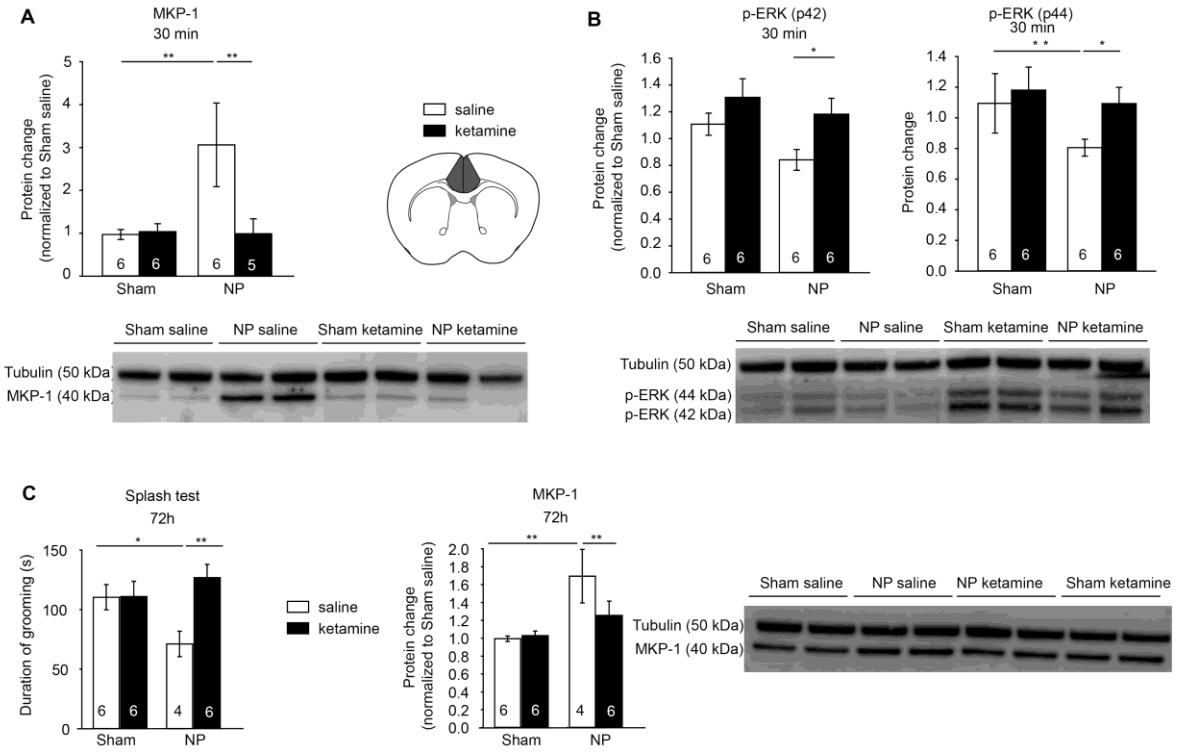

Fig. 3. The effect of ketamine on the MAPK pathway in the ACC. A) Western blot analysis showing an increase in MKP-1 protein level in the ACC of vehicle treated NP mice, and a decrease at 30 min after acute systemic ketamine treatment. B) Western blot results showing decreased pERK in the ACC of NP mice, which is restored 30 min after ketamine administration. C) Compared to the control group, the NP animals administered with ketamine still showed an increase in grooming duration in the splash test and a decrease in upregulated ACC MKP-1 at 72 h after treatment. Sample sizes are presented in brackets next to experimental groups.

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