Pharmacological Reports 71 (2019) 139–148

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

Kynurenic acid and zaprinast diminished CXCL17-evoked pain-related behaviour and enhanced morphine analgesia in a mouse neuropathic pain model

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ARTICLE INFO

Article history:
Received 6 June 2018
Received in revised form 3 September 2018
Accepted 2 October 2018
Available online 6 October 2018

Keywords:
CXCL17
Zaprinast
Kynurenic acid
Morphine

ABSTRACT

Background: The G protein-coupled receptor 35 (GPR35), is considered important for nociceptive transmission, as suggested by accumulating evidence. This receptor was discovered in 1998; however, a lack of pharmacological tools prevented a complete understanding of its function and how to exploit it therapeutically. We studied the influence of CXCL17, kynurenic acid and zaprinast on nociceptive transmission in naïve and neuropathic mice. Additionally, we investigated the influence of kynurenic acid and zaprinast on morphine effectiveness in neuropathic pain.

Methods: The chronic constriction injury (CCI) of the sciatic nerve in Swiss mice was performed. The CXCL17, kynurenic acid, zaprinast and morphine were injected intrathecally into naive and CCI-exposed mice at day 14. To evaluate tactile and thermal hypersensitivity, the von Frey and cold plate tests were used, respectively.

Results: Our results have shown, for the first time, that administration of CXCL17 in naïve mice induced strong pain-related behaviours, as measured by von Frey and cold plate tests. Moreover, we demonstrated that kynurenic acid and zaprinast diminished CXCL17-evoked pain-related behaviours in both tests. Kynurenic acid and zaprinast reduced thermal and tactile hypersensitivity developed by sciatic nerve injury and strongly enhanced the effectiveness of morphine in neuropathy.

Conclusions: Our study highlights the importance of GPR35 as a receptor involved in neuropathic pain development. Therefore, these results suggest that the modulation of GPR35 could become a potential strategy for the treatment of neuropathic pain.

Introduction

Neuropathic pain is a serious clinical problem, principally because of the weak efficacy and numerous adverse side effects of opioids [1,2]. Pain associated with neuropathy develops as a result of nervous system damage; however, the mechanism remains unknown despite numerous studies. Patients suffering from neuropathic pain symptoms exhibit ongoing spontaneous and evoked pain [3]. The mechanisms involved in the development of neuropathy are complex [4–6]; however, the participation of chemokines in this phenomenon seems to be very important and still unclear [7–12]. First, fractalkine (CX3CL1) has been shown to induce neuropathic pain [13,14]. Recently, it was postulated that chemokines C-C (CCL2, CCL3, CCL5, CCL7), C-X-C (CXCL1, CXCL5, CXCL9, CXCL12) and X-C (XCL1) motif chemokine ligands also play a crucial role in the development of neuropathic pain [10,15–25]. Therefore, it is important to determine the role of CXCL17 in nociceptive transmission. In 2015, studies have provided evidence that chemokine (C-X-C motif) receptor 8 (CXCR8), also named GPR35, is a receptor for chemokine (C-X-C motif) ligand 17 (CXCL17) [26]. GPR35 is 7-Transmembrane receptor that transmits function *via* interactions with $G_{ai/o}$, G_{a13}, and beta-arrestin [27–30]. GPR35 is expressed in the nervous systems in both neuronal and non-neuronal cells, including glia, and is therefore suggested to be important for nociceptive transmission [31,32]. Recently, it has been shown that GPR35 agonists, such as kynurenic acid or zaprinast beneficially influence the nociceptive transmission [33].

We hypothesized that GPR35 is important for nociception under neuropathic pain. We compare the influence of CXCL17 with the endogenous (kynurenic acid) and exogenous (zaprinast) ligands for GPR35 on nociceptive transmission in naïve mice. An additional aim of this study was to determine how zaprinast and

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https://doi.org/10.1016/j.pharep.2018.10.002
1734-1140/

kynurenic acid influence neuropathic pain-related behaviours in CXCL17- and sciatic nerve injury-evoked neuropathic pain. Finally, we asked whether kynurenic acid and zaprinast might improve the effectiveness of opioids, such as morphine, in a mouse neuropathic pain model.

Materials and methods

Animals

Adult male Albino Swiss mice (Charles-River, Germany; 20–25 g) were housed in groups of six in cages with sawdust bedding under a standard 12 h/12 h light/dark cycle (lights on at 06.00 a.m.); food and water were available ad libitum. Experiments were carried out according to the recommendations of the International Association for the Study of Pain [34] and the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Local Bioethics Committee (Krakow, Poland, permission numbers 1210/2015&333/2018).

Chronic constriction injury

The chronic constriction injury (CCI) model was performed according to Bennett and Xie [35] and previous studies from our laboratory [12,38,37,39]. The surgical procedure was performed under isoflurane anaesthesia. Briefly, an incision was made below the right hipbone, parallel to the sciatic nerve. The sciatic nerve was exposed, and three ligatures (4/0-silk) were tied loosely around the nerve distal to the sciatic notch with 1 mm spacing, until a brief twitch in the respective hind limb was observed. After CCI, mice developed tactile/thermal hypersensitivity - the behavioural experiments were conducted on the day 14.

Behavioural tests

von Frey test

Tactile hypersensitivity was measured using von Frey filaments (Stoelting, Wood Dale, IL, USA), ranging from 0.6 to 6 g according to our earlier work [11,12,36]. Animals were placed in plastic cages with a wire mesh floor, allowing them to move freely. They were allowed to acclimate to this environment for approximately 5-15 min prior to testing. The von Frey filaments in ascending order were applied through the mesh floor to the midplantar surface of the injured hind paw. Each probe was applied to the foot until it started to bend. The ipsilateral and contralateral paws in CCI mice (or both hind paws in naïve mice) were tested 2–3 times and a mean value was calculated. The time interval between consecutive applications of filaments was at least 5 s.

Cold plate test

Sensitivity to noxious thermal stimuli was assessed using a cold/hot plate analgesia meter from Columbus Instruments, according to our earlier published work [12,23,38]. The latency was defined as the amount of time it took for the hind paw to begin to shake after the mouse was placed on a cold plate (2 °C). In CCI mice, the injured paw reacted first in all cases. In naive mice the reaction of any hind paw was noted. The cut off latency for this test was 30 s.

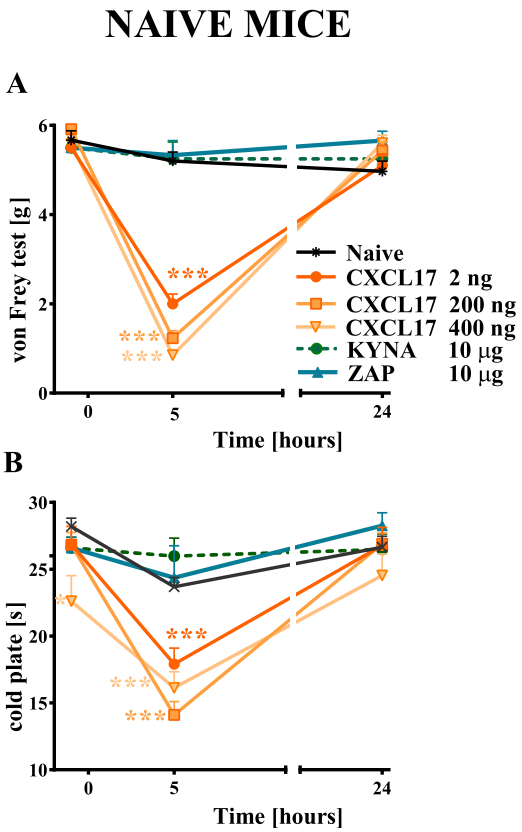

Fig. 1. The effects of the administration of single CXCL17, kynurenic acid and zaprinast on nociceptive transmission in naive mice. The effects of single intrathecal administration of chemokine (C-X-C motif) ligand 17 (CXCL17; 2 ng, 200 ng or 400 ng/5 µl), kynurenic acid (KYNA; 10 µg) and zaprinast (ZAP; 10 µg) on mechanical (von Frey test; A) and thermal (cold plate test; B) hypersensitivity were measured at 5 and 24 h after administration. Data are presented as the means ± SEM (6–18 mice per group), and the results were evaluated using one-way ANOVA followed by Bonferroni *post hoc* test for comparisons of selected pairs; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared the naïve animals *versus* all groups at respective timepoints.

Pharmacological studies

Intrathecal administration

Intrathecal (*it*) administration is a standard procedure in our laboratory [10,12,23] and is performed using a Hamilton syringe with a thin needle, as previously described [39]. Substances that were used in the experiments were injected into the lumbar portion of the spinal cord (L5-L6) in a volume of 5 μl, and the tail reflex was an indicator of correct administration.

Single *it* administration of CXCL17, zaprinast, and kynurenic acid in naive mice. CXCL17 was attained from R&D Systems (USA) and was dissolved in water for injection. After reconstitution, CXCL17 was singly administered *it* to naïve mice in the following doses: 2 200, and 400 ng/5 μl. Zaprinast and kynurenic acid were attained from Tocris (Janki, Warszawa) and were dissolved in DMSO and were singly administered *it* to naïve mice at a dose of 10 μg/5 μl. The kynurenic acid was administered intrathecally because is hardly able to cross the blood–brain barrier [40] and this type of administration for pain treatment was recommended by others [41,42]. The behavioural tests were performed 5, and 24 h following injection (Fig. 1).

Single *it* CXCL17 administration preceded by kynurenic acid and zaprinast injection in naive mice. In Figs. 2 and 3, naïve mice received kynurenic acid (10 μg/5 μl) and zaprinast (10 μg/5 μl). Next, two hours after substance administration, behavioural tests were conducted, and mice received CXCL17 (2 ng/5 μl) following the testing. The behavioural tests were performed 1.5, 5 and 24 h after CXCL17 injection (or 3.5, 7 and 26 h after kynurenic acid and zaprinast administration) (Scheme on Figs. 2 A/3A).

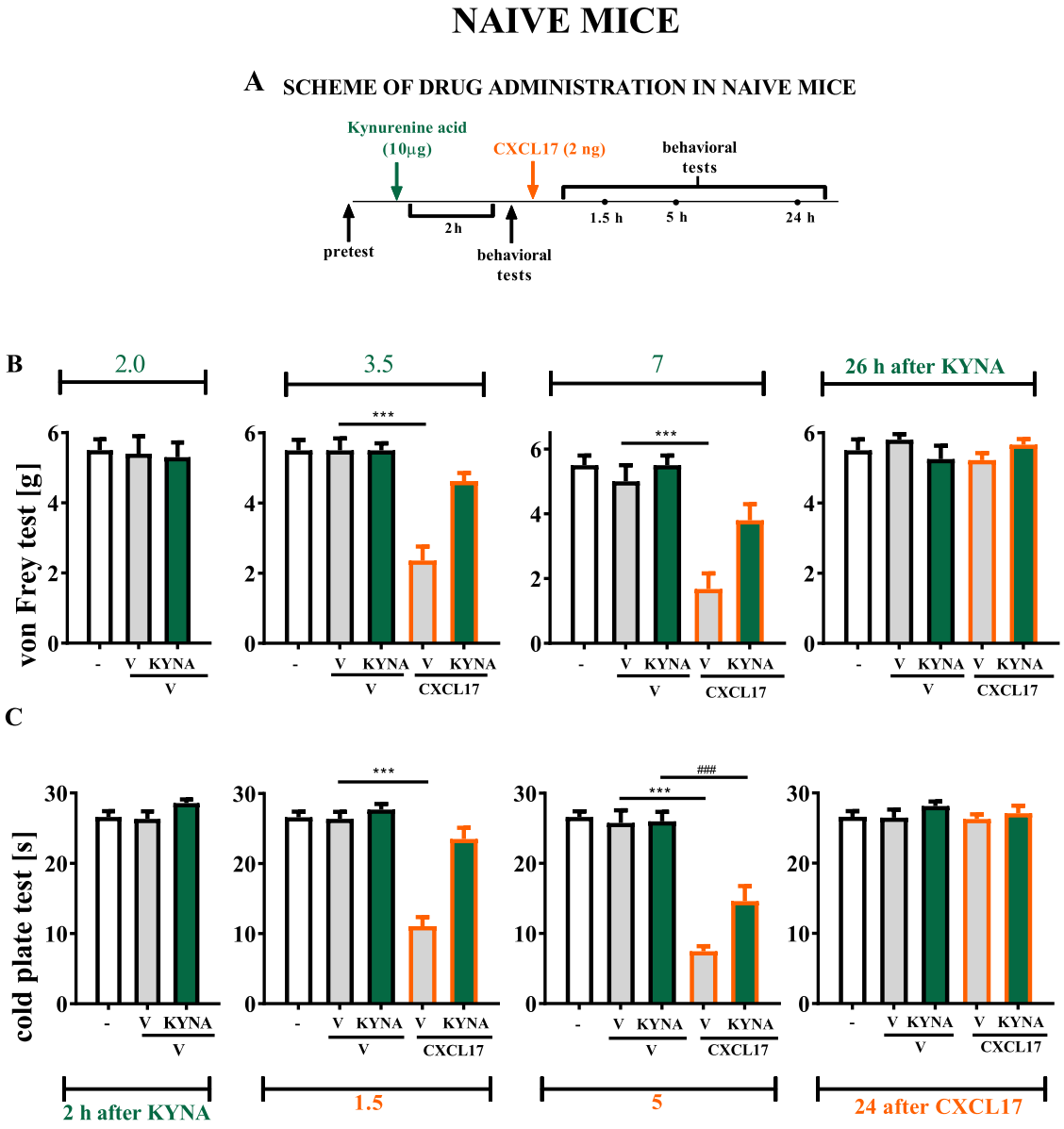

Fig. 2. The effects of single chemokine (C-X-C motif) ligand 17 (CXCL17, 2 ng) administration preceded by kynurenic acid (KYNA, 10 μg) injection in naïve mice. Behavioural tests were performed 2 h after intrathecal KYNA administration and at 1.5, 5 and 24 h after CXCL17 intrathecal administration (A). Mechanical (von Frey test; B) and thermal (cold plate test; **C**) hypersensitivity were measured. Data are presented as the means ± SEM (5 mice per group), and the results were evaluated with the use of one-way ANOVA followed by Bonferroni test for comparisons of selected pairs at respective timepoints. $^{***}p < 0.001$ compared the V+V- *vs.* V + CXCL17-treated naïve mice; $^{\#}p < 0.05$ and $^{\#\#\#}p < 0.001$ compared KYNA+V- *vs.* KYNA + CXCL17-treated naïve mice. Abbreviations: KYNA, kynurenic acid; V, vehicle.

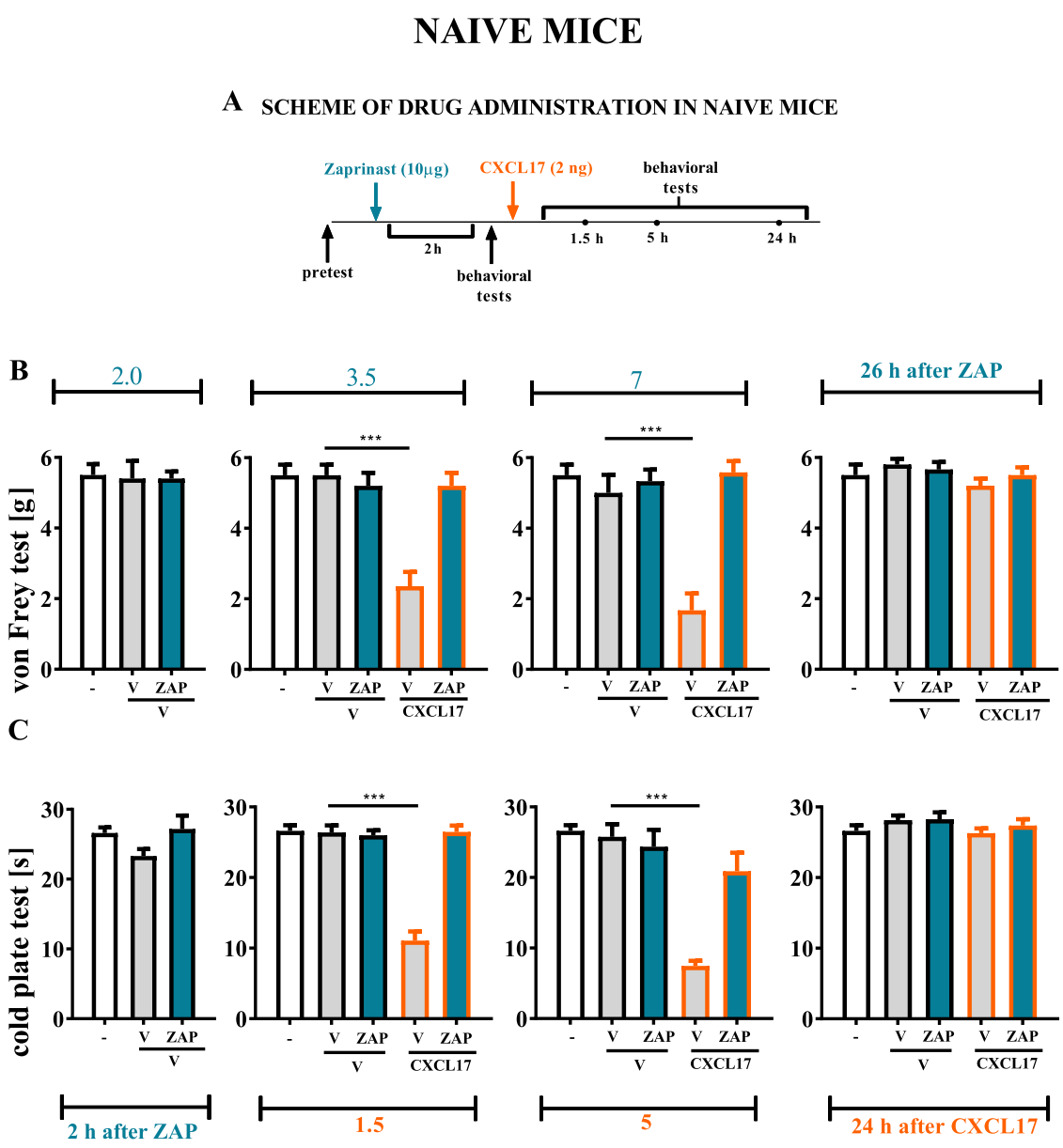

Fig. 3. The effects of single chemokine (C-X-C motif) ligand 17 (CXCL17, 2 ng) administration preceded by zaprinast (ZAP, 10 μg) injection in naïve mice. Behavioural tests were performed 2 h after intrathecal ZAP administration and at 1.5, 5 and 24 h after CXCL17 intrathecal administration (A). Mechanical (von Frey test; B) and thermal (cold plate test; C) hypersensitivity were measured. Data are presented as the means ± SEM (5–6 mice per group), and the results were evaluated with the use of one-way ANOVA followed by Bonferroni test for comparisons of selected pairs at respective timepoints. ***$p < 0.001$ compared the V+V- *vs.* V + CXCL17-treated naïve mice. Abbreviations: ZAP, zaprinast; V, vehicle.

Single *it* administration of CXCL17, zaprinast and kynurenic acid in mice with CCI-induced neuropathy. CXCL17 was obtained from Tocris (Janki, Warsaw) and reconstituted in water for injection. After reconstitution, CXCL17 was singly administered *it* to mice on day 14 after CCI in the following doses: 200 and 400 ng/5 μl. Additionally, each mouse in the control group was injected with 5 μl of water. The behavioural tests were performed 1.5 and 5 h following CXCL17 injection (Fig. 4).

Zaprinast and kynurenic acid were obtained from Tocris (Janki, Warsaw) and dissolved in dimethyl sulfoxide (DMSO). After reconstitution, zaprinast (0.5, 1, 2.5, 5 and 10 μg/5 μl) and kynurenic acid (0.5, 1, 5, 10 and 20 μg/5 μl) were singly administered *it* to mice on day 14 after CCI. Additionally, the control group was injected with 5 μl of DMSO. The behavioural tests were performed 0.5 and 2 h following injection of zaprinast and kynurenic acid (Fig. 5).

Single *it* administration of zaprinast and kynurenic acid with morphine in mice with CCI-induced neuropathy. Morphine (2.5 μg/5 μl) was obtained from Sigma-Aldrich (USA) and dissolved in water for injection. Morphine was singly administered *it* 1.5 h after injection of zaprinast and kynurenic acid (2.5 μg/5 μl and 5 μg/5 μl, respectively) on day 14 after CCI. Mice from the control group were injected with 5 μl of water. The behavioural tests were first performed 1.5 h following zaprinast and kynurenic acid injection and then repeated 30 min after morphine administration (scheme in Fig. 6A).

Data analysis

The behavioural data are presented as the means ± SEM Inter-group differences were analysed by ANOVA followed by

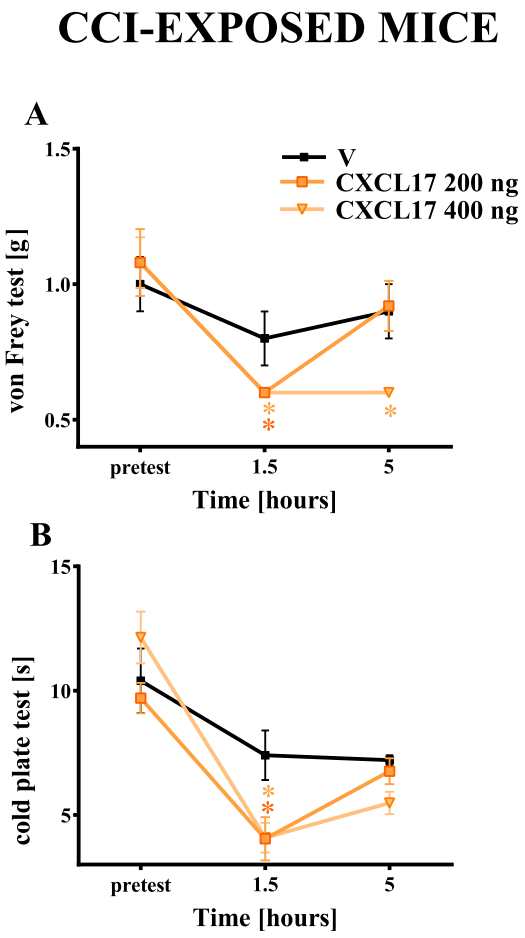

Fig. 4. The effects of (C-X-C motif) ligand 17 (CXCL17) administration on nociceptive transmission on day 14 after chronic constriction injury (CCI) of the sciatic nerve in mice. The effects of single intrathecal administration of CXCL17 (200 ng and 400 ng/5 μl) on mechanical (von Frey test; A) and thermal (cold plate test; B) hypersensitivity were measured at 1.5 and 5 h after administration. Data are presented as the means ± SEM (4–12 mice per group), and the results were evaluated using one-way ANOVA followed by Bonferroni *post hoc* test for comparisons of selected pairs; $^{*}p < 0.05$ compared to the V-treated CCI-exposed mice. Abbreviations: V, vehicle.

Bonferroni's multiple comparison test, and more details are given in the figure legends. All graphs were prepared using GraphPad Prism 7.0.

Results

Effects of single it *administration of CXCL17, kynurenic acid and zaprinast on nociceptive transmission in naïve mice*

Single *it* administrations of CXCL17, kynurenic acid and zaprinast in naïve mice were given. The influence of these substances on the development of hypersensitivity to mechanical and thermal stimuli was measured by von Frey (Fig. 1A) and cold plate (Fig. 1B) tests, respectively, at 5, and 24 h after administration. CXCL17 (2, 200 and 400 ng) caused the development of strong mechanical and thermal hypersensitivity, and the effect was diminished after 24 h. Five hours following the injection of the highest dose (400 ng), the reactions to both thermal and mechanical stimuli reached a maximum, and the two other doses induced similar responses. Therefore, for the rest of the experiments, we chose to use the 2 ng dose of CXCL17. Two-way ANOVA confirmed a significant interaction ($F = 12.88$; $p < 0.0001$) between the treatment type and time following the injections. In contrast, kynurenic acid (KYNA; 10 μg) and zaprinast (ZAP;10 μg) injection did not cause any effect in naïve animals as measured until 24 h after administration.

Effects of single it *CXCL17 administration preceded by kynurenic acid injection on nociceptive transmission in naive mice*

Our results indicated that single intrathecal administration of kynurenic acid (10 μg) has no effect on hypersensitivity, as measured by von Frey (Fig. 2B) and cold plate (Fig. 2C) tests in naïve mice 2 h after kynurenic acid injection. Single intrathecal administration of 2 ng CXCL17 was given 2 h after intrathecal injection of kynurenic acid, and behavioural tests were conducted 1.5, 5 and 24 h after CXCL17 administration (Fig. 2A). At 1.5 and 5 h following CXCL17 administration, strong mechanical and thermal hypersensitivity was observed. Kynurenic acid prevented the CXCL17-induced hypersensitivity, as assessed at 1.5 h in both tests. However, this effect was no longer observed at 5 h after CXCL17 injection.

Effects of single CXCL17 it *administration preceded by zaprinast injection on nociceptive transmission in naïve mice*

Our results demonstrated that single intrathecal administration of zaprinast (10 μg) has no effect on hypersensitivity, as measured by von Frey (Fig. 3B) and cold plate (Fig. 3C) tests at 2 h after zaprinast injection. Single intrathecal administration of 2 ng CXCL17 was given 2 h after the zaprinast injection, and behavioural tests were conducted 1.5, 5 and 24 h after CXCL17 administration (Fig. 3A). CXCL17 induced strong hypersensitivity to mechanical

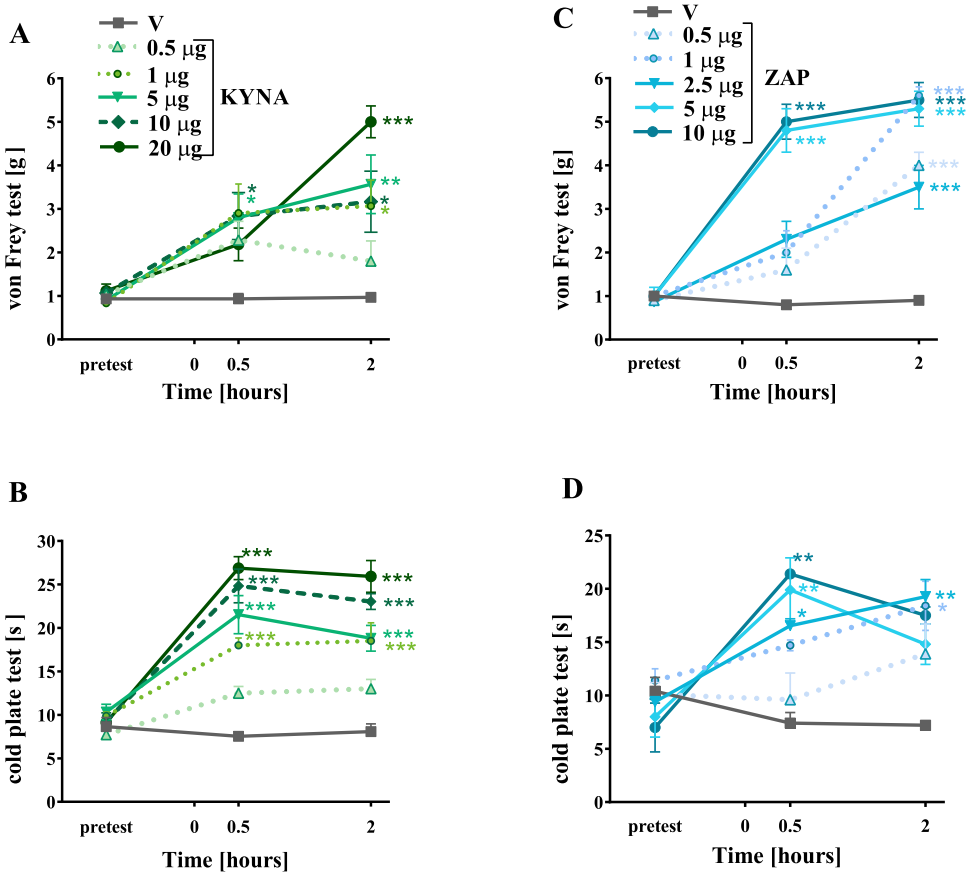

Fig. 5. The effects of the administration of single kynurenic acid and zaprinast on nociceptive transmission on day 14 after chronic constriction injury (CCI) of the sciatic nerve in mice. The effects of single intrathecal administration of kynurenic acid (KYNA; 0.5, 1, 5, 10 and 20 μg/5 μl) and zaprinast (ZAP; 0.5, 1, 2.5, 5 or 10 μg/μl) on mechanical (von Frey test; A,C) and thermal (cold plate test; B,D) hypersensitivity. Data are presented as the means ± SEM (4–12 mice per group), and the results were evaluated using one-way ANOVA followed by Bonferroni *post hoc* test for comparisons of selected pairs at respective timepoints; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the vehicle-treated CCI-exposed mice. Abbreviations: KYNA, kynurenic acid; ZAP, zaprinast; V, vehicle.

and thermal stimuli, as measured at 1.5 and 5 h after administration. Zaprinast prevented the CXCL17-induced hypersensitivity in both tests, as assessed at 1.5 and 5 h after the CXCL17 injection.

Effects of single CXCL17 it *administration on nociceptive transmission in the CCI-exposed mice*

Single *it* administration of CXCL17 (200 and 400 ng) was given on day 14 after CCI. We observed that CXCL17 dose-dependently enhanced the CCI-evoked hypersensitivity to mechanical and thermal stimuli, as measured by von Frey (Fig. 4A) and cold plate (Fig. 4B) tests. For the dose of 400 ng, the effect was still observed after 5 h, but only with the von Frey test.

Effects of single kynurenic acid and zaprinast it *administration on nociceptive transmission in CCI-exposed mice*

Single *it* administration of kynurenic acid (0.5, 1, 5, 10 or 20 μg) or zaprinast (0.5, 1, 2.5, 5 or 10 μg) was given on day 14 after CCI. We observed a dose-dependent analgesic effect of kynurenic acid or zaprinast on CCI-evoked hypersensitivity to mechanical and thermal stimuli, as measured by von Frey (Fig. 5A,C) and cold plate (Fig. 5B, D) tests, respectively, at 0.5 and 2 h after administration.

Effect of single administration of kynurenic acid or zaprinast on morphine analgesia in the CCI-exposed mice

A single *it* injection of morphine (2.5 μg) attenuated mechanical and thermal hypersensitivity at day 14 after CCI (Fig. 6B–E). Single intrathecal administration of kynurenic acid (5 μg) enhanced morphine-induced analgesia, as assessed by von Frey (Fig. 6B) and cold plate (Fig. 6C) tests. The same effects were observed after single zaprinast (2.5 μg) *it* administration (Fig. 6D, E).

Discussion

The results of the current study demonstrated for the first time that intrathecal administration of CXCL17 in naïve mice induced pain-related behaviours, which were abolished by kynurenic acid and zaprinast administration. Moreover, kynurenic acid and zaprinast diminished pain-related behaviours due to neuropathic pain and enhanced the effectiveness of morphine. Our results provide new evidence that zaprinast (exogenous) evoked similar effects as kynurenic acid (endogenous), indicating that agonists of GPR35 can effectively diminish neuropathic pain-related behaviours. Our data allow us to hypothesize that GPR35 is an interesting

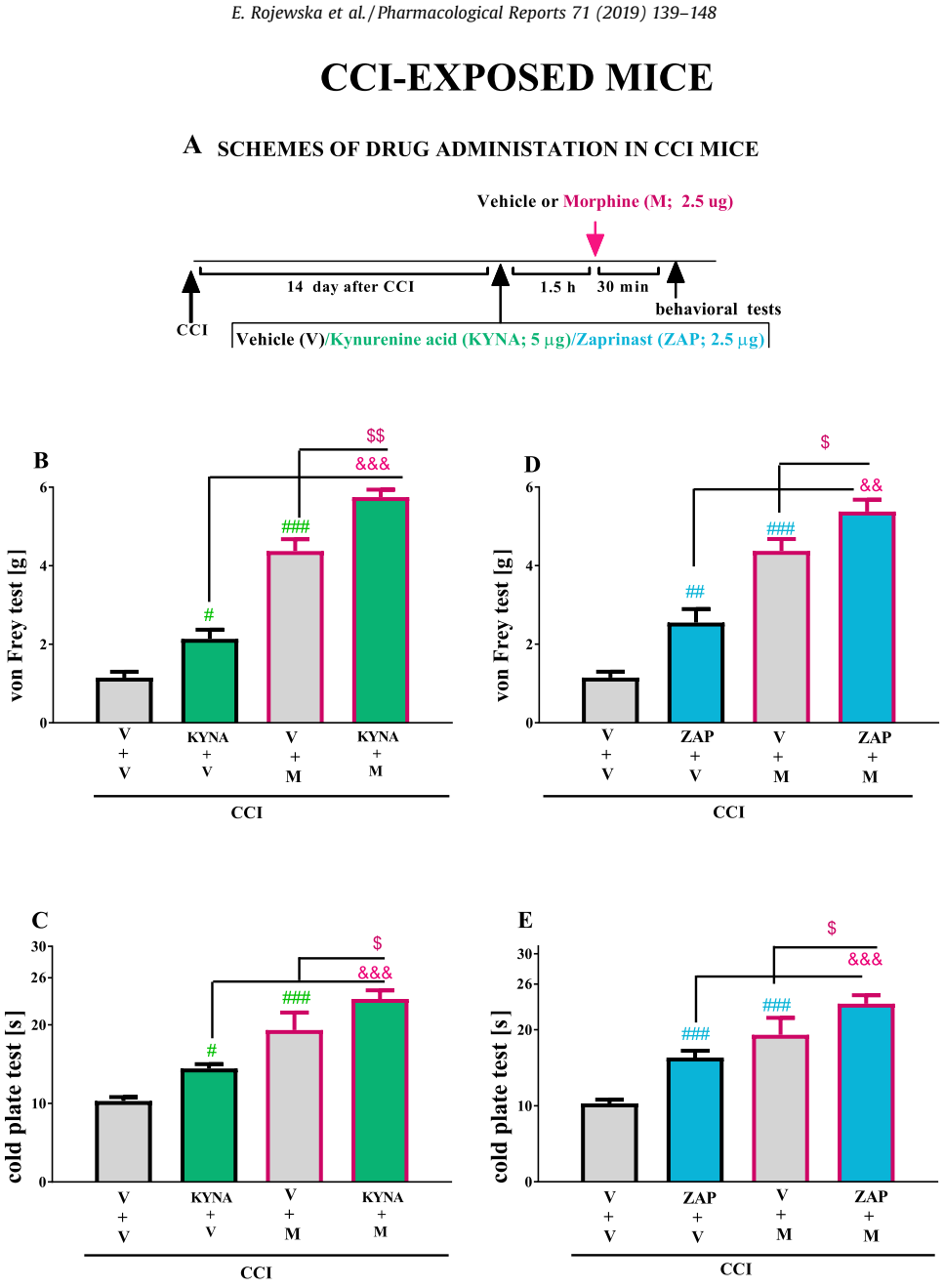

Fig. 6. The influence of single administration of kynurenic acid and zaprinast on the analgesic effects of morphine on day 14 after chronic constriction injury (CCI) of the sciatic nerve in mice. Mechanical (von Frey test; B,D) and thermal (cold plate test; C,E) hypersensitivity were measured at 1.5 h after kynurenic acid (KYNA 5 μg/μl) or zaprinast (ZAP; 2,5 μg/μl) intrathecal injections, and then morphine (M - 2.5 μg/5 μl *it*) was administered. The behavioural tests were conducted 0.5 h after opioid injection (A). The data are presented as the means ± SEM (7–12 mice per group); the inter-group differences were analysed using one-way analysis of variance ANOVA with Bonferroni's multiple comparison test; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ indicate differences compared with the V+V-treated CCI-exposed group; $^{\&}p < 0.05$, $^{\&\&}p < 0.01$ and $^{\&\&\&}p < 0.001$ indicates differences compared with the ZAP/KYNA+V-treated *vs.* ZAP/KYNA + M-treated CCI-exposed group; and $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ and $^{\$\$\$}p < 0.001$ indicates differences compared with the V+M-treated *vs.* ZAP/KYNA + M-treated CCI-exposed group. Abbreviations: M, morphine; KYNA, kynurenic acid; ZAP, zaprinast; V, vehicle.

target for new analgesic agents during neuropathic pain development.

GPR35 expression has been identified within discrete regions of the nervous system, including the spinal cord [43–48]. Importantly, GPR35 is expressed not only in neurons but also in spinal glial cells [43]. Unfortunately, changes in the GPR35 protein levels are very difficult to study because highly selective commercial antibodies are not available for Western blot analysis. Maravillas-Montero et al. [26] and Guo et al. [49] proved that CXCL17 may act *via* GPR35, however recent *in vitro* studies suggested that also another receptors for CXCL17 may exist [50,51]. The CXCL17 first, it was found to be involved in tumour angiogenesis [52–55] and to be co-regulated with vascular endothelial growth factor [55], but its role in nociceptive transmission has not studied, to the best of our knowledge. For the first time, we have shown in these experiments that intrathecal administration of CXCL17 in naive mice led to the development of strong tactile and thermal hypersensitivity. This effect is not surprising, as previous research has shown that other chemokines from the CXC group, such as CXCL1, CXCL4, CXCL5, CXCL9, CXCL10 and CXCL12, have similar properties after intrathecal administration in mice [10]. Moreover, CXCL1 was shown to be upregulated in a spinal nerve ligation model [56] and CXCL4, CXCL9, CXCL10 and CXCL12 were upregulated after sciatic nerve injury [57]; Kwiatkowski et al. [in preparation] and CXCL13 after infraorbital and spinal nerve ligation [58,59]. The observed pronociceptive properties of CXCL17, which is a strong

macrophage/microglia chemoattractant [26,60], are very important and may play a role in the development of neuropathy. Presently, it is known that peripheral nerve damage led to the influx and activation of microglia/macrophages [5,36,61–63] and that these cells contribute to the secretion of many pronociceptive mediators [61,64].

Kynurenic acid is a product of the normal metabolism of the amino acid L-tryptophan and is without any doubt considered to be an endogenous agonist of GPR35 [45,46,65], however is also a noncompetitive antagonist at the glycine site of the NMDA receptor [66–69] and an antagonist at ionotropic NMDA (as well as AMPA and kainate) glutamate receptors [41,70]. It has been shown that kynurenic acid exerts anticonvulsant effects and neuroprotective activity and is synthesized mainly in astroglial cells [71–74]. In our present study, we have shown that intrathecal administration of kynurenic acid reduced mechanical and thermal hypersensitivity in a sciatic nerve injury model in mice. These results correspond with previous reports showing that in rat neuropathic pain models, kynurenic acid administered intrathecally reversed the tactile hypersensitivity [75]. Moreover, kynurenic acid has analgesic properties in mice/rats pain models [33,45,47,76,77]. Similar results were observed with zaprinast, which is a high-affinity synthetic ligand of GPR35 [27,44,48,78–81]. In 2005, Yoon et al. [82] showed that zaprinast dose-dependently reduced the number of flinches in a formalin pain model in rats. Analgesic effects of zaprinast were later confirmed in other rat and mouse inflammatory pain models [33,45]. In our study, zaprinast also revealed analgesic properties with neuropathic pain, similar to others [43–48,83]. Our studies provide the first evidence that kynurenic acid and zaprinast injection diminished CXCL17 pronociceptive properties in naïve mice. This may be explained with the fact that the activation of GPR35 with zaprinast, kynurenic acid or CXCL17 leads to the distinct modulation of Ca^{2+} levels. In 2013, Southern et al. [84] showed that kynurenic acid and zaprinast reduced Ca^{2+} mobilization, while in 2015, Maravillas-Monetro et al. [26] provided evidence that in contrast, CXCL17 increased Ca^{2+} mobilization. Recently published *in vitro* results of Amir et al. [50] and Park et al. [51] suggest that perhaps CXCL17 exerts its effects also through the unknown yet receptor. In our experiments the pronociceptive properties of CXCL17 were not completely blocked, which may suggest that CXCL17 act *via* multiple receptors. However, this issue needs to be examined in the future.

Further, our study provides the first evidence that zaprinast and kynurenic acid administration not only prevented the development of thermal and mechanical hypersensitivity but also enhanced morphine antinociceptive properties. Morphine is considered to be one of the most effective analgesic drugs [5,61,62,85,86], however, the changes that lead to the development of neuropathic pain are also responsible for the reduction of its effectiveness in clinical use. The mechanism underlying this phenomenon is still not fully understood. Additionally, in a neuropathic pain model, we demonstrated that the analgesic properties of morphine are lower with neuropathy than in naïve animals [25,87]. For the first time, we have shown in this study that single administration of zaprinast enhances the analgesic activities of morphine. This result is in agreement with previous reports from Yoon et al. [88] and Heo et al. [89], who have also shown that zaprinast enhanced morphine effectiveness in a formalin model. We hypothesize that the increased effectiveness may be due to the ability of zaprinast to inhibit microglial activation in neuropathic pain (Rojewska et al. submitted). It is well known that activated microglia change their gene expression profiles and produce pronociceptive factors (IL-1beta [90]; IL-18 [87]; and many others) that are responsible for the loss of opioid analgesia. It has been found that substances that diminish microglia activation, such as inhibitors (pentoxifylline and minocycline [91]; and antagonists of chemokine receptors (CCR5-maraviroc; [25,92], CCR2- RS504393 [17]; CXCR3-NBI-74330; [57], suppressed the development of neuropathic pain. Recent experimental data supported the potential of combination pharmacotherapy for neuropathic pain. Therapeutic benefits may include greater efficacy, lower dosage and fewer adverse effects. Our data provide new evidence that GPR35 is a promising target for diminishing neuropathic pain and enhancing opioid analgesic effects.

Author contributions

E. Rojewska—Study Design, Data Collection, Statistical Analysis, Data Interpretation, Acceptance of final manuscript version, Literature Search and Funds Collection.

K. Ciapała—Study Design, Data Collection, Statistical Analysis, Data Interpretation, Acceptance of final manuscript version and Literature Search.

J. Mika—Study Design, Data Collection, Statistical Analysis, Data Interpretation, Acceptance of final manuscript version, Literature Search and Funds Collection.

Acknowledgments

This work was supported by grants from the National Science Centre, Poland: SONATA 2015/17/D/NZ4/02284, OPUS 11 2016/21/B/NZ4/00128 and by statutory funds from the Institute of Pharmacology Polish Academy of Sciences.

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