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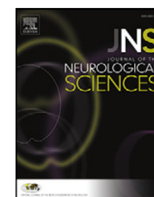

Blocking PAR2 attenuates oxaliplatin-induced neuropathic pain via TRPV1 and releases of substance P and CGRP in superficial dorsal horn of spinal cord

Kun Chen, Zhi-Fa Zhang, Ming-Feng Liao, Wen-Long Yao, Juan Wang, Xue-Ren Wang *

Department of Anesthesiology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei, China
[a] *Tongji Medical College, Wuhan, Hubei, China*

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ABSTRACT

Oxaliplatin (OXL) is a third-generation chemotherapeutic agent commonly used to treat metastatic digestive tumors; however, neuropathic pain is one of the main limiting complications of OXL. The purpose of this study was to examine the underlying mechanisms by which neuropathic pain is induced by OXL in a rat model. Our results demonstrated that blocking spinal proteinase-activated receptor 2 (PAR2) and transient receptor potential vanilloid 1 (TRPV1) attenuated pain responses evoked by mechanical stimulation and decreased the releases of substance P and CGRP in the superficial dorsal horn of the spinal cord. The attenuating effect on mechanical pain was significantly smaller in OXL-rats than that in control rats. Blocking PAR2 also attenuated a heightened cold sensitivity evoked by OXL; whereas blocking TRPV1 had little effects on OXL-evoked hypersensitive cold response. Our data also showed that OXL increased the protein expressions of PAR2 and TRPV1 in the superficial dorsal horn. In addition, blocking PAR2 decreased TRPV1 expression in OXL-rats. Overall, our data suggest that upregulated expression of PAR2 in the superficial dorsal horn contributes to mechanical hyperalgesia and cold hypersensitivity; whereas amplified TRPV1 plays a role in regulating mechanical hyperalgesia, but not cold hypersensitivity after administration of OXL. We further suggest that TRPV1 is likely one of the signaling pathways for PAR2 to play a role in regulating OXL-induced neuropathic pain.

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1. Introduction

Pain is one of the most common and distressing symptoms suffered by patients with progression of cancer [1]. Cancer pain mainly arises from a tumor compressing or infiltrating tissue; from nerve and other changes caused by a hormone imbalance or immune response; and/or from treatments and diagnostic procedures [1,2]. Of note, radiotherapy and chemotherapy may produce painful conditions that persist long after treatment has ended [1,3,4]. Thus, how to effectively manage cancer pain-related to these therapies also becomes an important issue for treatment and management of cancer patients in clinics.

Oxaliplatin (OXL) belonging to organoplatinum compound is a third-generation chemotherapeutic agent commonly used to treat the cancer [5]. Especially, it has significant activities against advanced and/or metastatic digestive tumors, but one of the main limiting complications of OXL is painful neuropathy [6]. It is noted that the signs of neuropathy start with paresthesia, followed by hyperesthesia [2]. Also, a heightened cold sensitivity is another complication in cancer patients with OXL treatment [6].

In general, the neuropathic pain is likely to result from disorders of the peripheral nervous system and/or the central nervous system (spinal cord and brain) [7,8]. Treatment options for these abnormal sensations have been restricted, partly due to our poor understanding of the underlying mechanisms by which neuropathic pain is induced by chemotherapeutic agents.

The levels of numerous neurotransmitters and related receptors in sensory neurons–dorsal root ganglion neurons that supply primary afferent fibers contribute to neuropathic pain [9,10]. The superficial dorsal horn of the spinal cord is the first synaptic site for pain transmission from peripheral afferent nerves to the central nervous system [10]. The releases of neurotransmitters, namely substance P and calcitonin gene-related peptide (CGRP) [11–13], within the dorsal horn also play an important role in regulating pain responses [10]. In addition, results of the prior studies by using animal models suggest a role for proteinase-activated receptor 2 (PAR2) [14,15] and transient receptor potential vanilloid 1 (TRPV1) [11–13] at the spinal levels in regulating the releases of neurotransmitters including substance P and CGRP, two essential substrates considered to be responsible for common pain (i.e., due to inflammation and nerve damages) or neuropathic pain related to diabetes.

In a rat model, injection of OXL produces mechanical hyperalgesia and allodynia [16,17]. OXL can induce mechanical hyperalgesia after

* Corresponding author at: Department of Anesthesiology, Tongji Hospital, Huazhong University of Science and Technology, 1095 Jie-Fang Road, Wuhan, Hubei 430030, China.
E-mail address: wangxueren@hotmail.com (X.-R. Wang).

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initiation of the chemotherapy regimen in rats. The signs of mechanical hyperalgesia were ablated after discontinuation of OXL [16,17]. In addition, the cold hypersensitivity was observed in animals with injection of OXL [16,17]. Thus, the rat model has been widely employed to study the mechanisms of neuropathic pain induced by chemotherapy such as OXL [16,18].

In the current study, we specifically examined the effects of blocking spinal PAR2 and TRPV1 on mechanical hyperalgesia and cold sensitivity in OXL-rats and control rats. Also, we examined the expression of PAR2 and TRPV1 in the superficial dorsal horn of both OXL-rats and control rats. Moreover, we examined the role for PAR2 and TRPV1 in regulating the levels of substance P and CGRP in the dorsal horn of the spinal cord in OXL-rats and control rats.

2. Methods

2.1. Animal

All animal protocols were approved by the Animal Care and Use Committee of Tongji Medical College and were carried out in accordance with the guidelines of the International Association for the Study of Pain. Male Wistar rats weighing 150–180 g were obtained from the Center for Experimental Animal Sciences of this institution. The rats were housed in individual cages with free access to food and water and were kept in a temperature-controlled room (25 °C) on a 12/12 h light/dark cycle.

2.2. A model of neuropathic pain

Oxaliplatin (Tocris Biosci, UK) was dissolved in a 5% glucose solution at a final concentration of 2 mg/ml. Acute neurotoxicity was induced in rats by an intraperitoneal (i.p.) injection of oxaliplatin (6 mg/kg/day), as described previously [16,17]. Control rats received the same volume of i.p. injection of vehicle. Experiments were performed 3 days after injections.

2.3. Intrathecal catheter for administration of drugs

Rats were anesthetized by intraperitoneal injection of sodium pentobarbital (60 mg/kg) in order to implant intrathecal catheter for administration of drugs. Briefly, one end of polyethylene-10 tubing was inserted intrathecally through an incision in the cisternal membrane and advanced 7–9 cm caudal until the tip of the catheter was positioned at the lumbar spinal level (L5 to L6). The other end of the intrathecal tubing was sutured to the musculature and skin at the incision site and externalized to the back of the rat. In each experiment, a Hamilton microsyringe (250 μl) was connected to the intrathecal tubing and used to deliver 100 μl of dimethyl sulfoxide (DMSO) as control, FSLLRY-NH2 (PAR2 antagonist, 10 μg) [25] and iodo-resiniferatoxin (i-RTX, TRPV1 antagonist, 10 μg) [19] (obtained from Sigma-Aldrich, St. Louis, MO, USA).

2.4. Behavioral test

To quantify the mechanical sensitivity of the hindpaw, rats were placed in individual plastic boxes and allowed to acclimate for >30 min. Mechanical paw withdrawal threshold (PWT) of rat hindpaw in response to the stimulation of von Frey filaments was determined. A series of calibrated von Frey filaments (ranging from 0.5 to 18.0 g) were applied perpendicularly to the plantar surface of the hindpaw with a sufficient force to bend the filaments for 60 s or until paw withdrew. In the presence of a response, the filament of next lower force was applied. In the absence of a response, the filament of the next greater force was applied. To avoid injury during tests, the cutoff strength of the von Frey filament was 18 g. The tactile stimulus producing a 50% likelihood of withdrawal was determined using the "up-down" method [20]. Each trial was repeated 2 times at approximately 2 min intervals. The values from two trials were averaged as the force produced a withdrawal response.

In order to assess a cold avoidance behavior, Thermal Place Preference System (Coulburn Instruments, Whitehall, PA, USA) was used to perform the thermal place preference test. Two connecting metal plates were surrounded by a plastic enclosure. The first plate was kept at neutral temperature (25 °C) and the second plate was kept at cold temperature (12 °C). The test was performed in darkness and each session lasted 3 min. During the session, the animals were left free to explore both plates. The time spent on the cold plate during the entire session was recorded using an infrared camera connected to a computer in order to determine cold avoidance behavior. To better control behavior test, the rats were repeatedly placed on the apparatus with both plates held at room temperature (25 °C) during 3 min a few days before the beginning of the experiment. Note that rats spent an equal amount of time on each plate under these conditions, suggesting that animals showed no place preference. In addition, to avoid learning or any place preference unrelated to cold, the temperature of the plates were inverted between two consecutive sessions.

2.5. Western blot analysis

The superficial dorsal horn tissues (L4–L6) were removed under an anatomical microscope and total protein was then extracted by homogenizing samples in ice-cold immunoprecipitation assay buffer. The lysates were centrifuged and the supernatants were collected for measurements of protein concentrations. After being denatured, the supernatant samples containing 20 μg of protein were loaded onto 4–20% Mini-PROTEAN TGX gels and electrically transferred to a polyvinylidene fluoride membrane. The membrane was blocked and incubated overnight with primary antibody (mouse anti-PAR2 and anti-TRPV1 at 1:200, Cayman Chemical Co.). Next, the membranes were washed and incubated with an alkaline phosphatase conjugated anti-mouse secondary antibody (1:1000). The immunoreactive proteins were detected by enhanced chemiluminescence. The bands recognized by the primary antibody were visualized by exposure of the membrane onto an X-ray film. The membrane was stripped and incubated with mouse anti-β-actin to show equal loading of the protein. Then, the film was scanned and the optical density of PAR2/TRPV1 and β-actin bands was analyzed using the Scion Image software.

2.6. ELISA measurements

To examine the levels of substance P and CGRP in the superficial dorsal horn of the spinal cord (L4–L6), ELISA methods were employed. Substance P was measured using substance P ELISA kit following the manufacturer's instructions (Abcam Co., Cambridge, MA). Briefly, the diluted tissue supernatant (100 μl) was placed in a 96-well goat anti-mouse IgG-coated plate and incubated for 2 h. After incubation, the plate was washed using the provided washing buffer, and the color was developed by adding PNPP (200 μl) substrate after 45 min and determined by an ELISA plate reader. The amount of substance P was calculated by using a substance P standard curve. In the similar way, the CGRP content of the samples (100 μl supernatant) was determined using a commercial CGRP ELISA kit (Cayman Chemical Co.). Briefly, the diluted samples were placed in a 96-well plate incubated with pre-coated anti-rat IgG antibody overnight, washed and developed, and quantified [21].

2.7. Statistical analysis

All the data were analyzed using a two-way repeated-measures analysis of variance (ANOVA). Values were presented as means ± standard error of mean (SEM). For all the analyses, differences were

considered significant at $P < 0.05$. All the statistical analyses were performed by using SAS for Windows version 10.0 (SAS Institute, Cary, NC).

3. Results

Overall, OXL injection significantly decreased PWT as compared with glucose injection. PWT was 9.13 ± 0.40 g in control rats (n = 22) and 3.63 ± 0.22 g in OXL-rats (n = 24, $P < 0.05$ vs. control rats).

Fig. 1A shows that intrathecal injection of FSLLRY-NH2 (10 μg) significantly increased PWT in control rats and OXL-rats, as compared with vehicle control. In addition, the percentage increase of PWT evoked by blocking PAR2 receptors was smaller in OXL-rats (n = 12) than that in control rats (n = 10). i.e. PWT was increased by 53% in OXL-rats ($P < 0.05$ vs. control rats) and 85% in control rats 20 min after injection of FSLLRY-NH2; and PWT was increased by 58% in OXL rats ($P < 0.05$ vs. control rats) and 80% in control rats 30 min after injection of FSLLRY-NH2.

OXL injection also significantly diminished % time spent on the cold plate as compared with glucose injection. The percentage time spent was 55 ± 3% in control rats (n = 22) and 33 ± 2% in OXL-rats (n = 24, $P < 0.05$ vs. control rats). Fig. 1B further shows that blocking PAR2 in the superficial dorsal horn of the spinal cord by intrathecal injection of FSLLRY-NH2 (10 μg) significantly attenuated cold sensitivity in control rats (n = 10) and OXL-rats (n = 12).

Likewise, Fig. 2A demonstrates that intrathecal injection of i-RTX (10 μg) significantly increased PWT in control rats and OXL-rats, as compared with vehicle control. The percentage increase of PWT evoked by blocking TRPV1 receptors was smaller in OXL-rats (n = 12) than that in control rats (n = 12). i.e. PWT was increased by 59% in OXL-rats ($P < 0.05$ vs. control rats) and 81% in control rats 20 min after injection of i-RTX; and PWT was increased by 60% in OXL rats ($P < 0.05$ vs. control rats) and 77% in control rats 30 min after injection of i-RTX. However, Fig. 2B shows that intrathecal injection of i-RTX (10 μg) failed to attenuate cold sensitivity in control rats (n = 12) and OXL-rats (n = 12) since no significant differences in % time spent on the cold plate were observed after i-RTX injection ($P > 0.05$, i-RTX vs. vehicle control for both control rats and OXL-rats).

Fig. 3 illustrates that the protein expression of PAR2 and TRPV1 in the superficial dorsal horn of the spinal cord was significantly increased in OXL-rats (n = 8) compared with control rats (n = 8). The optical density of PAR2 was 0.96 ± 0.10 in control rats and 1.75 ± 0.12 in OXL-rats ($P < 0.05$ vs. control rats); and the optical density of TRPV1 was 0.98 ± 0.12 in control rats and 1.67 ± 0.15 in OXL-rats ($P < 0.05$ vs. control rats). In addition, in a subset of experiments (n = 6), the protein expression of TRPV1in the superficial dorsal horn of the spinal cord was significantly attenuated 3 h after intrathecal injection of FSLLRY-NH2 (10 μg).

In additional experiments, the effects of OXL treatment on the levels of substance P and CGRP in the superficial dorsal horn of the spinal cord

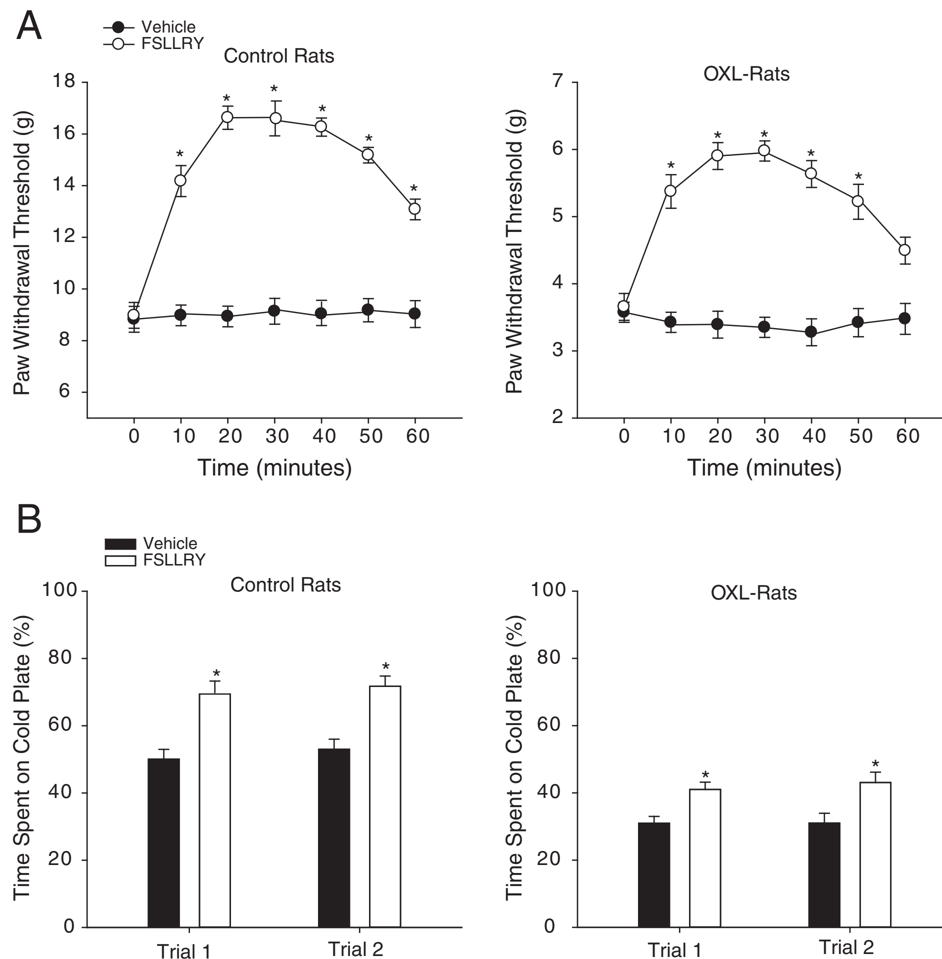

Fig. 1. (A) Effects of blocking PAR2 on paw withdrawal threshold (PWT) in control rats and OXL-rats. Intrathecal injection of FSLLRY-NH2 (10 μg) increased PWT in control rats and OXL-rats, as compared with vehicle injection. Note that the percentage increases of PWT evoked by attenuation of PAR2 were smaller in OXL-rats than that in control rats. The number of rats = 10 in control rats and = 12 in OXL-rats. (B) Effects of blocking PAR2 on cold sensitivity expressed as time spent on the cold plate (%) in control rats and OXL-rats. Intrathecal injection of FSLLRY-NH2 increased % time spent in control rats and OXL-rats, as compared with vehicle injection. Two trials were performed for this experiment. The number of rats = 10 in control rats and = 12 OXL-rats. In panels A& B, data are expressed as mean ± SEM. *$P < 0.05$ vs. vehicle control.

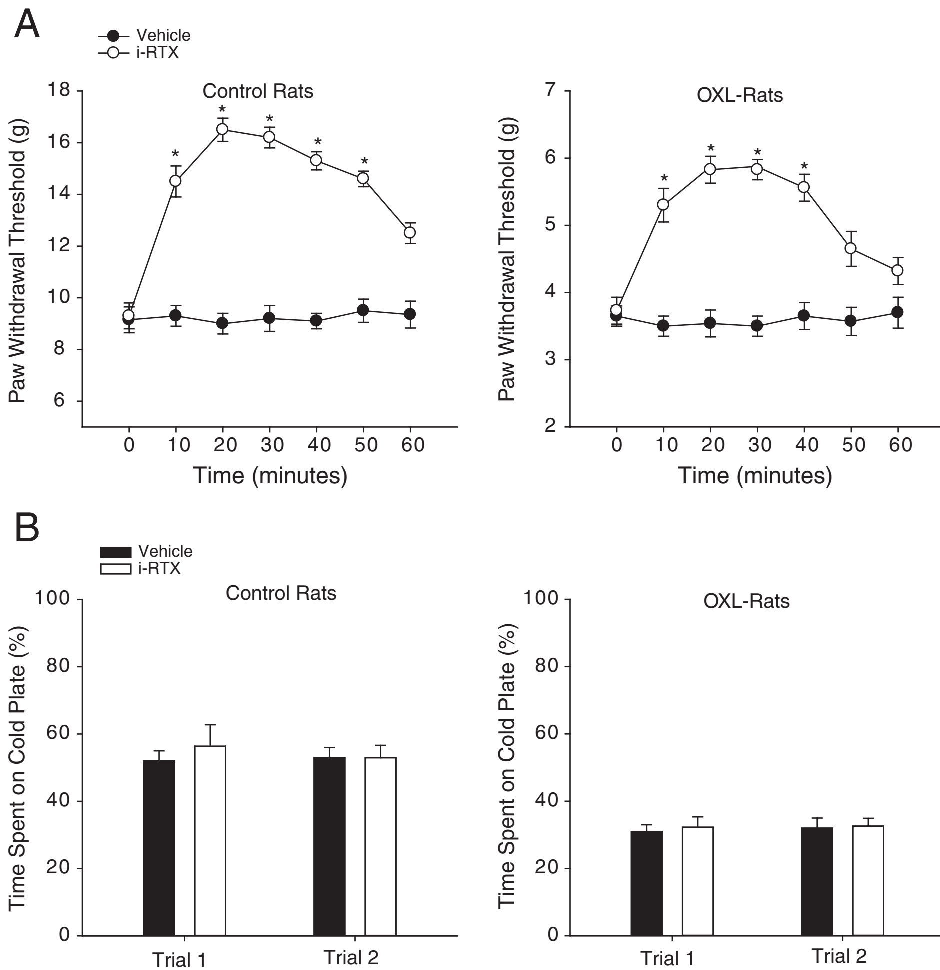

Fig. 2. (A) Effects of blocking TRPV1 on paw withdrawal threshold (PWT) in control rats and OXL-rats. Intrathecal injection of i-RTX (10 μg) increased PWT in control rats and OXL-rats, as compared with vehicle injection. % increases of PWT evoked by attenuation of i-RTX were smaller in OXL-rats than that in control rats. Data are expressed as mean ± SEM. *$P < 0.05$ vs. vehicle control. The number of rats = 12 in each group of rats. (B) Intrathecal injection of i-RTX failed to alter % time spent in control rats and OXL-rats, as compared with vehicle injection. The number of rats = 12 in each group of rats.

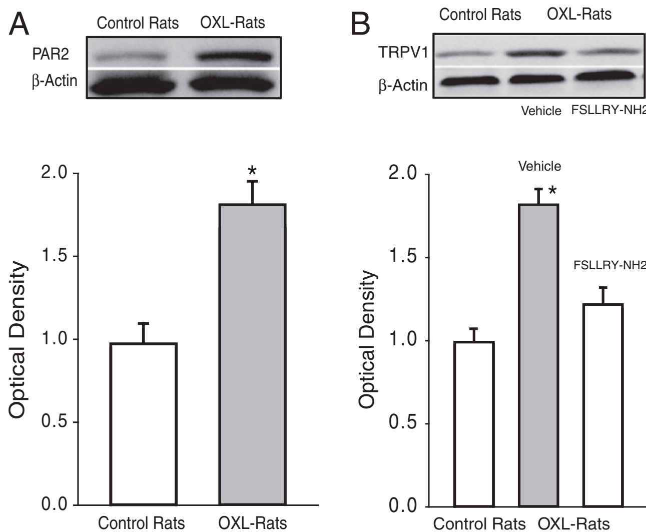

Fig. 3. Effects of OXL-treatment on the protein expression of PAR2 and TRPV1 in the superficial dorsal horn of the spinal cord. Top panel is representative of typical bands and bottom panel indicates averaged data obtained from control rats and OXL-rats. Data are expressed as mean ± SEM. *$P < 0.05$ vs. control rats (in panel A), and vs. control rats and OXL-rats with FSLLRY-NH2 (in panel B). N = 8 in control and OXL group with vehicle injection; n = 6 in OXL group with FSLLRY-NH2. β-Actin was used as equal loading control.

were examined as shown in Fig. 4. Substance P and CGRP were significantly increased in OXL-rats (n = 12) as compared with control rats (n = 12). Also, blocking individual PAR2 and TRPV1 by intrathecal injection of 10 μg of FSLLRY-NH2 (n = 8) and 10 μg of i-RTX (n = 10) significantly attenuated amplifications in substance P and CGRP evoked by OXL injection. Note that a greater inhibitory effect on substance P was observed by FSLLRY-NH2.

4. Discussion

Prior studies have shown that injection of OXL induces neuropathic pain in rats [16,17]. The animals show mechanical hyperalgesia and cold hypersensitivity. These abnormalities are maintained for several days. Using the similar intervention, we observed significantly declined threshold to evoke mechanical withdrawal (indicated as PWT) and less time (%) spent on the cold plate three days after OXL injection in our current study (Figs. 1&2). This is consistent with the results reported previously [16–18]. Also, there was no significant difference observed in body weight gain between control rats and OXL-rats and no deterioration in general status was observed after injection of this dosage of OXL. Our results further demonstrated that intrathecal injection of PAR2 antagonist, FSLLRY-NH2 and TRPV1 antagonist, i-RTX significantly increased PWT in control rats and OXL-rats, and the effects of blocking PAR2 and TRPV1 were significantly smaller in OXL-rats (Fig. 1&2). Consistently, our results also demonstrated that expression of PAR2 and TRPV1 protein was upregulated in the superficial dorsal horn of the

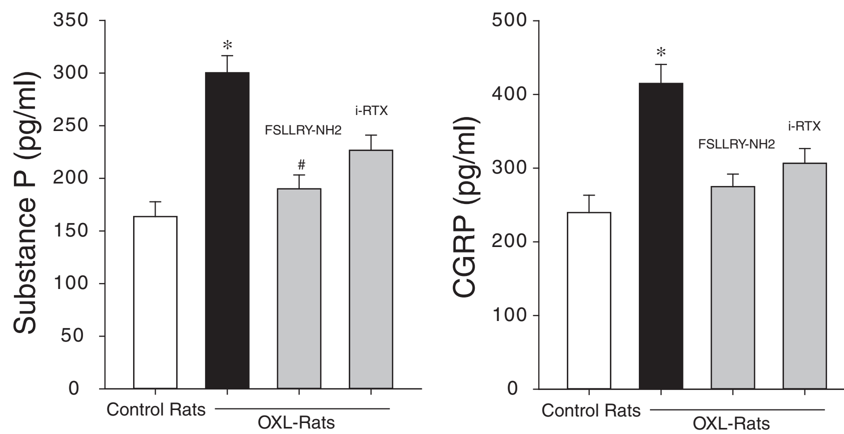

Fig. 4. The levels of substance P and CGRP in the superficial dorsal horn of the spinal cord. OXL-treatment significantly increased substance P and CGRP as compared with controls and blocking PAR2 and TRPV1 by intrathecal injection FSLLRY-NH2 (10 μg) and i-RTX (10 μg) significantly attenuated the enhancement in substance P and CGRP evoked by OXL. Note that a greater inhibitory effect on substance P was observed by FSLLRY-NH2. Data are expressed as mean ± SEM. *$P < 0.05$, indicated OXL-rats (n = 12) vs. control rats (n = 12) and OXL-rats with FSLLRY-NH2 (n = 8) and i-RTX injection (n = 10). # $P < 0.05$, indicated OXL-rats with FSLLRY-NH2 injection vs. with i-RTX injection.

spinal cord of OXL-rats as compared with control animals (Fig. 3). Importantly, FSLLRY-NH2 attenuated TRPV1 expression. Furthermore, our results showed that FSLLRY-NH2 increased % time spent on the cold plate in both groups of animals (Fig. 1); however, the effects were not observed after intrathecal injection of i-RTX (Fig. 2). In addition, the levels of substance P and CGRP, two important neurotransmitters engaged in the neuropathic pain, were significantly increased in the superficial dorsal horn of OXL-rats and intrathecal injection of FSLLRY-NH2 and i-RTX significantly attenuated the increased substance P and CGRP (Fig. 4). FSLLRY-NH2 had a greater effect on substance P than i-RTX did. Thus, our data suggest that amplified expression of PAR2 and TRPV1 in the superficial dorsal horn of the spinal cord is likely engaged in OXL-induced mechanical hyperalgesia and the releases of substance P and CGRP. Upregulated expression of PAR2, but not TRPV1 plays a role in regulating cold hypersensitivity evoked by OXL. We further suggest that TRPV1 is likely one of the signaling pathways for PAR2 to play a role in regulating OXL-induced neuropathic pain.

PARs are a family member of G-protein-coupled receptors and are activated by a proteolytic mechanism [22]. Among the four members of PARs, PAR2 is largely distributed in various tissues, including skin, gastrointestinal, cardiovascular, and respiratory systems. Of note, ~60% of DRG neurons at the L4–L6 levels contain PAR2 [23,24]. Stimulation of PAR2 by peripheral or central administration of non-inflammatory doses of PAR2 agonists evokes mechanical and thermal hyperalgesia in rodents [14,15]. These studies further suggest that the releases of substance P and CGRP [14,15] play a role in engagement of acute and chronic pain by activation of PAR2. In experimental animal models, the expression of PAR2 is upregulated in the dorsal horn of the spinal cord after chemotherapy (i.e., paclitaxel) and blocking spinal PAR2 eliminates mechanical and thermal hyperalgesia observed in animals with paclitaxel [25]. Nevertheless, to the best of our knowledge it has not been reported that PAR2 pathways specifically contributes to OXL-induced hyperalgesia and the underlying mechanisms responsible for the role of PAR2 in regulating OXL-evoked neuropathic pain. In the present study, we suggest that PAR2 has a regulatory effect on mechanical hyperalgesia and cold hypersensitivity evoked by OXL.

TRPV1 is a non-selective cation channel that can be activated by a wide variety of endogenous physical and chemical stimuli such as noxious heat, low pH (acidic conditions), endocannabinoid anandamide, N-oleyl-dopamine, and N-arachidonoyl-dopamine [26–28]. The activation of TRPV1 leads to a painful, burning sensation. TRPV1 receptors are found mainly in the nociceptive neurons of the peripheral nervous system, but they have also been described in the central nervous system including brain and spinal cord [29–32]. TRPV1 is involved in the transmission and modulation of pain (nociception), as well as in the integration of diverse painful stimuli [29–32]. Evidence further suggests the role for TRPV1 in regulating neuropathic pain in peripheral and central nervous systems [31]. The results of our current study support the specific role played by TRPV1 at the level of spinal cord in regulating mechanical hyperalgesia evoked by OXL. Nonetheless, our results showed that the cold hypersensitivity observed in OXL-rats was not attenuated by the blocking of spinal TRPV1 receptors.

Transient receptor potential ankyrin 1 (TRPA1) has a functional role in pain and neurogenic inflammation resulting from channel activation to a variety of compounds including pungent agents, irritant chemicals, reactive oxygen and nitrogen species, and products of oxidative stress-induced lipid peroxidation [33–37]. TRPA1 has been shown to co-localize with TRPV1 in subpopulations of dorsal root ganglion neurons [36] and is engaged in development of bradykinin-induced mechanical hypersensitivity and painfully cold temperatures [38,39]. Additional evidence supports the notion that TRPA1 mediates OXL-induced cold hypersensitivity [40]. We speculated that activation of TRPA1 is likely engaged in OXL-induced cold hypersensitivity since a prior study suggests that TRPA1 is one of PAR2 downstream pathways in regulating neuropathic pain [25].

Substance P and CGRP are excitatory neurotransmitters and (or) neuromodulators that are released in the spinal dorsal horn by the primary sensory afferents, thus contributing to the development of allodynia and hyperalgesia by facilitating the release of excitatory glutamate and aspartate from primary afferents [41]. It should be noted that substance P is restricted to A- and C-fiber nociceptors, the absence of CGRP immunoreactivity in the spinal cord may be linked to the absence of alteration of C-fibers [41]. In addition, an injection of OXL increases the amount of substance P and CGRP immunoreactivity and greater expression of substance P was observed likely via stimulation of A-fibers [17]. As noted, a recent work in human patients has shown that chronic OXL-induced pain is associated with dysfunction in A-, and C- types of primary afferent fibers and deficits in A- and C-fiber function appear to be specifically associated with the generation of pain [42]. Stimulation of TRPV1 in the dorsal horn alters the releases of substance P and CGRP [12,29]. Nevertheless, to the best of our knowledge there is a lacking evidence specifically showing the role played by TRPV1 in regulating the releases of spinal substance P and CGRP in a neuropathic pain model induced by OXL treatment. The results of this report suggest that substance P and CGRP regulated by TRPV1 at the spinal level contribute to OXL-induced neuropathic pain.

In conclusion, the data of the current study demonstrated that OXL intervention amplified the protein expressions of PAR2 and TRPV1 in

the superficial dorsal horn of the spinal cord as an important synaptic site responsible for pain transmission. In agreement with this, the injection of OXL increases substance P and CGRP in the dorsal horn via activation of PAR2 and TRPV1 and this contributes to mechanical hyperalgesia. PAR2 plays a role in regulating OXL-evoked cold hypersensitivity; whereas TRPV1 mechanisms are unlikely to contribute to cold hypersensitivity after OXL administration. It is likely that TRPV1 is one of the signaling pathways for PAR2 to play a role in regulating OXL-induced neuropathic pain. The results of this study will provide a base for the mechanisms responsible for OXL-induced neuropathic pain and further offer a strategy to target the peripheral nerve system for treatment and management of neuropathic pain often observed in cancer patients.

Conflict of interest

None.

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