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Research Paper

Tat-HA-NR2B9c attenuate oxaliplatin-induced neuropathic pain

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ABSTRACT

Oxaliplatin is a commonly used chemotherapy drug, which can produce acute and chronic peripheral neurotoxicity. Currently, there is no good therapeutic drug in clinic. Excessive stimulation of *N*-methyl-D-aspartate receptors (NMDARs) is crucial for the transmission of pain signals. However, directly inhibiting NMDARs can cause severe side effects because they have key physiological functions in the Central nervous system (CNS). Several years ago, we prepared a polypeptide Tat-HA-NR2B9c which can disturb NMDARs–postsynaptic density protein-95 (PSD-95) interaction. In this study, we studied whether Tat-HA-NR2B9c could be an effective treatment for oxaliplatin-induced neuropathic pain. To conform it, a rat model of oxaliplatin-induced neuropathic was established, and analgesic effect of Tat-HA-NR2B9c was studied. Here, we show that oxaliplatin induces the interaction of NMDARs with PSD-95. Uncoupling the complex by Tat-HA-NR2B9c has potent analgesic effect in oxaliplatin-induced cold hyperalgesia and mechanical allodynia without suppressing general behavioral. Tat-HA-NR2B9c neither inhibits NMDARs function nor impacts antitumor activity of oxaliplatin. Thus, this new drug may serve as a treatment for oxaliplatin-induced neuropathic pain, perhaps without major side effects.

1. Introduction

Oxaliplatin is a third-generation platinum chemotherapy drug that is widely used in the treatment of many solid tumors including bowel cancer, lung cancer, ovarian cancer and pancreatic cancer [Wahlman et al., 2018]. However, about 74% patients receiving oxaliplatin suffer from acute symptoms and 48% suffer from persistent symptoms [Alejandro et al., 2013]. Currently, there is no effective treatment for neuropathic pain caused by chemotherapy, which is due in part to the difficulty in translating findings obtained from preclinical rodent models of chemotherapy induced peripheral neuropathy (CIPN) to clinic [Shidahara et al., 2016]. CIPN is a common neurological complication and major concern in oncology practice, given the lack of effective treatment and the increasing number of cancer survivors [Zhou et al., 2016]. Thus, finding therapeutic targets and developing effective analgesics have been considered very meaningful to clinic.

Oxaliplatin is metabolized to oxalate and dichloro (1, 2-diaminocyclohexane) platinum [Pt (dach) Cl_2] [Graham et al., 2000]. Oxaliplatin and oxalate may alter voltage-gated Na^+ channels and cause peripheral nerve injury, cold hyperalgesia and mechanical allodynia [Grolleau et al., 2001; Sakurai et al., 2009]. Central sensitization is a high reactivity of the spinal dorsal horn neurons to sensory input, which is a mechanism leading to chronic pain [Woolf, 1983]. Central sensitization is important in the development and maintenance of chronic pain. Long lasting harmful peripheral stimulation can activate NMDARs, trigger intracellular signaling cascade in the dorsal sensory neurons [Mihara et al., 2011; Qu et al., 2009]. Thus, blockade of NMDARs should be logically effective. Unfortunately, NMDARs play an important role in neural circuit rebuilding. NMDA receptor antagonists exhibit good analgesic effects in animal models, but clinical applications are limited because they have significant side effects [Chaplan et al., 1997; Mao et al., 1993; Ren and Dubner, 1993]. PSD-95 is a scaffolding protein, that binds both NMDARs 2B subunits (NR2B) and neuronal nitric oxide synthase (nNOS). The macromolecular signaling complex couples NMDAR activity to the production of NO (nitric oxide) [Aarts et al., 2002]. NO has been reported to induce NMDA-induced hyperalgesia [Kitto et al., 1992]. Targeting PSD-95 may be an ideal therapeutic approach for pain treatment. Recently, we constructed a

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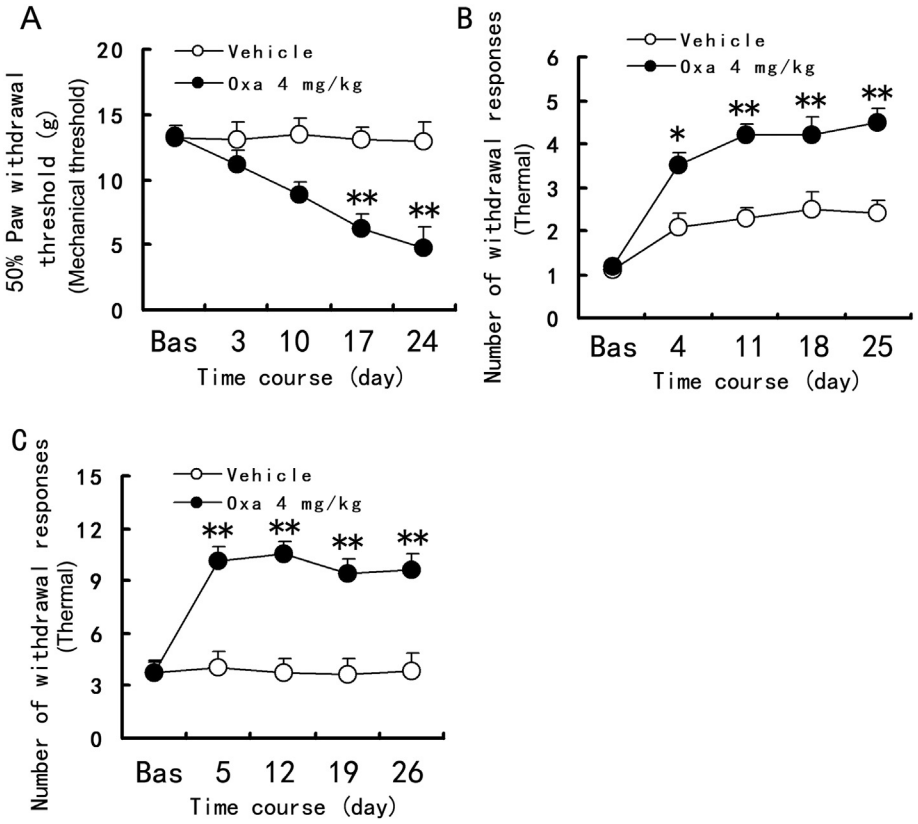

Fig. 1. Effects of oxaliplatin on mechanical allodynia (A), cold hyperalgesia (B, acetone test; C, cold plate test) in rats. Oxaliplatin (Oxa), Tat-HA-NR2B9c (9c). ($n = 10$ for vehicle, $n = 11$ for oxaliplatin). Data are mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. vehicle.

chimeric peptide Tat-HA-NR2B9c, containing the last 9 amino acids residues carboxyl of NR2B COOH-terminal, an influenza virus hemagglutinin epitope-tag and 11-mer Tat protein transduction domain. The chimeric peptide showed significant brain protection effect [Zhou et al., 2012; Zhou et al., 2015]. Here we show that NMDAR–PSD-95 interaction modulates oxaliplatin-induced pain. Dissociating NMDAR–PSD-95 coupling significantly attenuated oxaliplatin-induced neuropathic pain. Thus, we identify a novel approach to treat oxaliplatin-induced pain.

2. Materials and methods

2.1. Animals

All methods involved in animal were approved by the Institutional Animal Care and Use Committee of Nanjing University (Approval No., GY20160108), and all procedures involving animals were carried out in accordance with National Institute of Health guidelines for laboratory animals. Adult male Sprague-Dawley rats (220–250 g) were purchased from B&K Universal Group Limited, Shanghai. And 6-week-old male BALB/c mice (20–25 g) were purchased from Nanjing University Animal Center. All animals were housed at 22 ± 2°Con a 12 h light/dark cycle with free access to water and food.

2.2. Experimental design

Adult male Sprague-Dawley rats were randomized into four experimental groups: vehicle, oxaliplatin, oxaliplatin + Tat-HA-NR2B9c (50 ng), oxaliplatin + Tat-HA-NR2B9c (100 ng). Oxaliplatin was (Sigma-Aldrich, St Louis, Missouri, USA) dissolved in 5% glucose solution. In sham and oxaliplatin groups, 5% glucose solution or oxaliplatin (4 mg/kg) was, respectively, injected intraperitoneally (i.p.) twice a week for 4 weeks (on days 1, 2, 8, 9, 15, 16, 22, and 23). In Tat-HA-NR2B9c-treated groups, in addition to oxaliplatin injection, Tat-HA-NR2B9c was administered intrathecal injection on day 24, 25 and 26. Mechanical hyperalgesia measurement, acetone test and cold-plate test were measured on 24 days, 25 days and 26 days respectively.

2.3. Drugs

Tat-HA-NR2B9c was prepared in our laboratory [Zhou et al., 2012]. Oxaliplatin (Sigma-Aldrich, St Louis, Missouri, USA) was dissolved in 5% dextrose (1 mg/ml) and prepared fresh for daily use. Oxaliplatin was administered 4 mg/kg i.p. twice a week for 4 weeks. This kind of administration was proved safety [Cavaletti et al., 2001].

2.4. Intrathecal injection of Tat-HA-NR2B9c

The intrathecal injection was administered according to the procedure described previously with slight modification [Zhou et al., 2016]. Simply, rats were artificially restrained to maintain the position of the needle and then a 25-μl Hamilton syringe with a 30-gauge needle was used for intrathecal (i.t.) injection into the L5–6 interspace, eliciting a tail-flick. After injection, the syringe was held for a few seconds.

2.5. Mechanical hyperalgesia measurement

Mechanical hyperalgesia was measured by von Frey test [Mihara et al., 2011]. Each rat was placed in a transparent plastic box with a wire mesh and allowed them to get used to it for 30 min before testing. Von Frey filaments of varying forces (2–15 g) were applied serially to the paw using the up-down method. The 15 g filament was selected as the upper limit cutoff for testing. A positive response was noted if the paw was sharply withdrawn.