European Journal of Pharmacology 823 (2018) 27–34

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Full length article

Effects of ralfinamide in models of nerve injury and chemotherapy-induced neuropathic pain

Xiaonan Liang, Gang Yu*, Ruibin Su*

State Key Laboratory of Toxicology and Medical Countermeasures, Beijing Key Laboratory of Neuropsychopharmacology, Beijing Institute of Pharmacology and Toxicology, 27 Taiping Road, Beijing 100850, China

ARTICLE INFO

Keywords:
Neuropathic pain
Sodium channel blocker
Ralfinamide
Analgesic

ABSTRACT

Neuropathic pain is among the most common and difficult-to-treat types of chronic pain and is associated with sodium channel malfunction. The sodium channel blocker ralfinamide has exhibited potent analgesic effects in several preclinical pain models and in patients with mixed neuropathic pain syndromes (Phase II trials), but it failed to ameliorate neuropathic low back pain in Phase III trials. It is unclear whether ralfinamide is effective against neuropathic pain induced by specified etiologies. In the present study, the antinociceptive effects of ralfinamide in neuropathic pain models induced by spared nerve injury and chemotherapy were compared in a gabapentin-controlled manner. The effects of ralfinamide on physiological pain were evaluated in mechanical withdrawal, hot plate, and acetic acid writhing tests. We also investigated the effects of ralfinamide on cardiovascular function and locomotor activity. Oral ralfinamide dose-dependently alleviated spared nerve injury-induced allodynia in rats and mice. Ralfinamide increased mechanical withdrawal thresholds in oxaliplatin-induced and paclitaxel-induced neuropathic pain. Ralfinamide did not affect physiological pain, locomotion, or cardiovascular function. Together, ralfinamide attenuated mechanical allodynia in all the neuropathic pain models tested, with subtle differences in efficacy. The effect of ralfinamide is comparable to that of gabapentin, but with no interference in basal mechanical sensitivity. The present study supports the effectiveness of selective sodium channel blockade as an analgesic strategy, as well as the development of compounds similar to ralfinamide.

1. Introduction

Normally, pain is essential for preventing exposure to ongoing or impending tissue damage. In contrast, chronic pain transforms the physiological pain response into a debilitating and persistent disease (King and Vetter, 2014). Neuropathic pain, which arises from a lesion or dysfunction in the nervous system, is among the most common and difficult-to-treat types of chronic pain. According to recent epidemiological studies, the global prevalence of neuropathic pain is up to 8% (Bouhassira et al., 2008; Schmader, 2002). Currently, no available therapy provides sufficient pain relief without severe side effects (Gilron and Dickenson, 2014).

Sodium channels are key mediators of nerve and muscle function, facilitating sodium ion influx and thus generating action potentials in excitable cells. Dysregulated sodium channel expression and functioning in response to nerve injury and inflammation has been reported, and this leads to hyperexcitability in nociceptive neurons (Waxman and Zamponi, 2014; Mantegazza et al., 2010; Laedermann et al., 2015). Gain-of-function mutations of the SCN9A gene, which encodes $Na_v1.7$, cause inherited neuropathic pain in humans, whereas loss-of-function mutations result in a congenital indifference to pain without motor, cognitive, or cardiac deficits (Dib-Hajj et al., 2013). Therefore, pharmacological inhibition of sodium channels is an attractive strategy for altering the firing properties of afferent fibers to cure pain. Accordingly, some non-selective sodium channel-blocking local anesthetics have been used to treat neuropathic pain (Gilron and Dickenson, 2014). Many sodium channel-blocking anticonvulsants such as carbamazepine and lamotrigine are also demonstrably effective as analgesics for neuropathic pain (Zuliani et al., 2010). However, the existing sodium channel blockers have severe limitations, mainly due to their poor selectivity for sodium channel isoforms (England and de Groot, 2009).

Ralfinamide (NW-1029) is an α-aminoamide derivative with sodium channel blocking properties, acting both peripherally and centrally through $Na_v1.7$ and $Na_v1.8$ to control pain (Zhang et al., 2008). In rodent models, ralfinamide has been demonstrated to reverse inflammatory hyperalgesia and chronic constriction injury-induced mechanical allodynia, delay autonomy onset, and suppress autonomy scores (Zhang et al., 2008; Veneroni et al., 2003). Unsurprisingly, ralfinamide demonstrated a significant benefit

* Corresponding authors.
E-mail addresses: yg1st@163.com (G. Yu), ruibinsu@126.com (R. Su).

https://doi.org/10.1016/j.ejphar.2018.01.041
Received 25 August 2017; Received in revised form 29 December 2017; Accepted 25 January 2018
Available online 04 February 2018

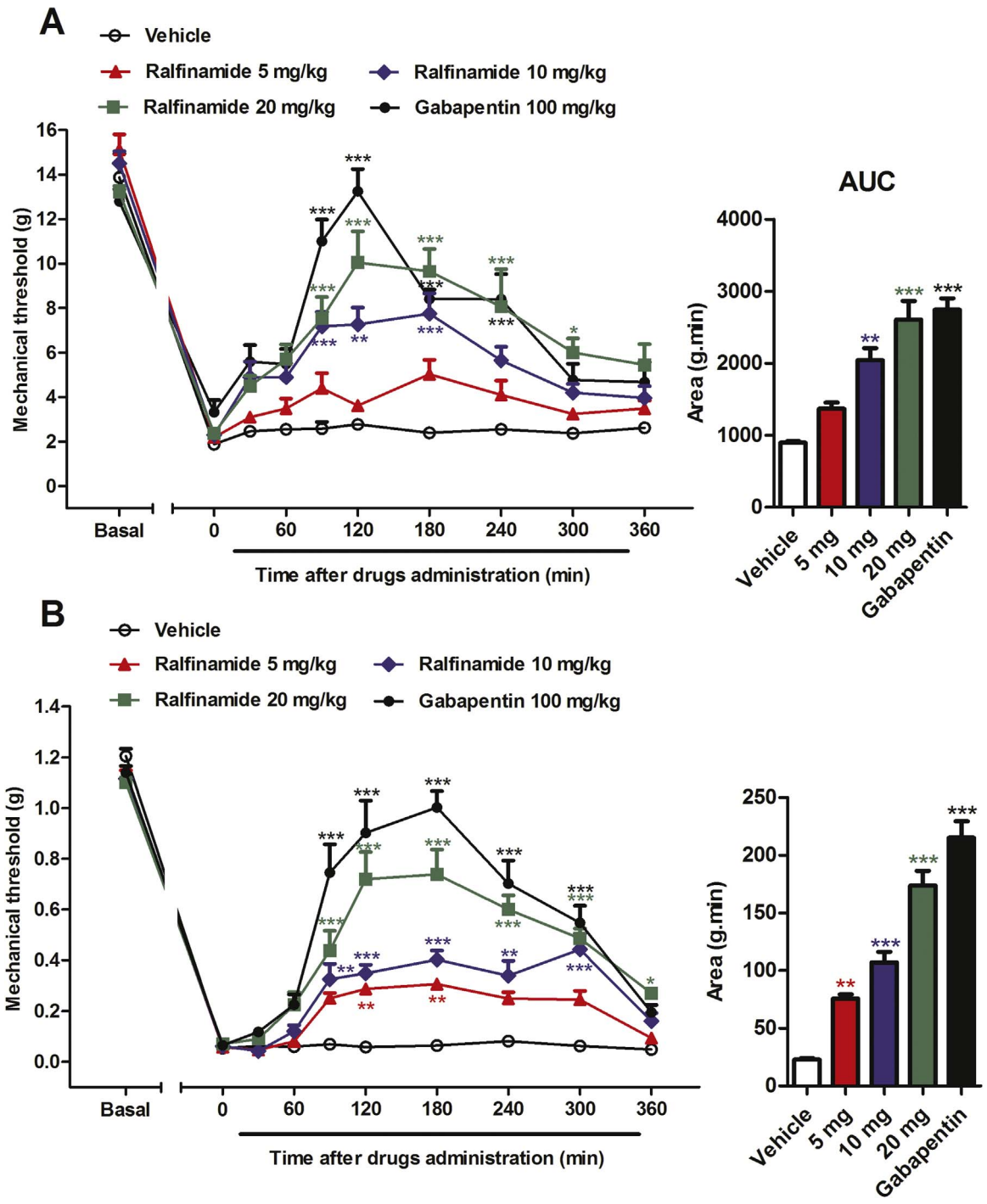

Fig. 1. Intragastric administration of ralfinamide attenuated spared nerve injury (SNI)-induced mechanical allodynia. (A) Ralfinamide (5, 10, and 20 mg/kg) exhibited dose-dependent and long-acting antinociceptive effects in SNI rats. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with vehicle alone-treated rats in repeated measures two-way ANOVA and Bonferroni post-hoc tests (n = 8 for vehicle group; n = 11 for gabapentin group; n = 6 for 5 mg/kg ralfinamide group; n = 12 for 10 mg/kg ralfinamide group; n = 14 for 20 mg/kg ralfinamide group). (B) Ralfinamide (5, 10, and 20 mg/kg) exhibited dose-dependent and long-acting antinociceptive effects in SNI mice. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with vehicle-treated mice in repeated measures two-way ANOVA and Bonferroni post-hoc tests (n = 8–10). Data are expressed as the mean ± SEM. The right panel of each figure shows the corresponding dose–response as AUC for different treatments between 0 and 360 min. $^{**}P < 0.01$, $^{***}P < 0.001$, compared with vehicle-treated animals in one-way ANOVA with Bonferroni post-hoc tests.

compared with placebo in Phase II trials (Zuliani et al., 2010). However, in Phase III trials, in which patients with at least moderate neuropathic low back pain were tested, there was no significant difference between ralfinamide and placebo (Newron Reports Italy, 2010), which ultimately led to termination of clinical research into ralfinamide. After analyzing previous data, we concluded that the observed discrepancies in ralfinamide-induced analgesia may be attributed to its inappropriate use in responder subgroups (Attal and Bouhassira, 2015; Goldberg et al., 2012), and ralfinamide may be effective in subdivided neuropathic pain models. To validate the efficacy of ralfinamide and clarify its potential indications, further comparison of its effects in subdivided pain models is required. Here, we report some other characteristics of ralfinamide, with emphasis on its analgesic effects in one trauma-induced and two chemotherapy-induced neuropathic pain models.