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Original Research

Berberine Alleviates Paclitaxel-Induced Neuropathy

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Key Words

berberine, paclitaxel, heat hyperalgesia, mice, neuropathic pain

Abstract

Objectives: Paclitaxel (PTX) as an anticancer drug used against solid cancers, possesses adverse reactions such as neuropathic pain which has confined its use. PTX-induced neuropathic pain is mediated via activation of oxidative stress. Berberine (BER), an isoquinoline phytochemical found in several plants, exerts strong antioxidant and painkilling properties. In the current study, we aimed to evaluate pain-relieving effect of BER in a mouse model of PTX-induced neuropathic pain.

Methods: This study was done using 42 male albino mice that were randomly divided into 6 groups (n = 7) as follow: Sham-operated (not treated with PTX), negative control group (PTX-treated mice receiving normal saline), BER 5, 10, and 20 mg/kg (PTX-treated mice receiving BER) and positive control group (PTX-treated mice receiving imipramine 10 mg/kg). Neuropathic pain was induced by intraperitoneal administration of four doses of PTX (2 mg/kg/day) on days 1, 3, 5 and 7. Then, on day 7, hot plate test was done to assess latency to heat to measure possible anti-neuropathic pain effect of BER.

Results: Four doses of PTX 2 mg/kg/day induced neuropathy that was reduced by BER at all time-points (i.e. 0, 30, 60, 90 and 120 min) after injection ($P < 0.001$ in comparison to control). The statistical analysis of data showed significant differences between groups ($P < 0.001$ in comparison to negative control), at 30, 60, 90 and 120 min after injection of BER 5, 10 and 20 mg/kg; in other words, 30, 60, 90 and 120 min after BER administration, neuropathic pain was significantly reduced as compared to normal saline-treated mice.

Conclusion: Altogether, our results showed that PTX could induce neuropathic pain as reflected by hyperalgesia and BER could alleviate PTX-induced thermal hyperalgesia.

1. Introduction

Peripheral neuropathy is considered one the main side effects of paclitaxel (PTX), an anti-cancer drug which is widely used to treat solid tumors (e.g. breast and ovarian cancer) [1, 2]. This dose-limiting neurotoxicity is observed in the form of hypoesthesia, par-

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esthesia, and distal extremities pain [3]. Moreover, higher doses of PTX are associated with hypoesthesia and anesthesia whereas lower doses induce hyperalgesia and allodynia [4-6]. Besides, following PTX administration, peripheral neuroinflammation as indicated by macrophage recruitment and increased cytokine/chemokine secretion [7, 8].

Berberine (BER) is a naturally occurring alkaloid (Figure 1) isolated from several plants such as *Coptis chinensis, Coptis japonica, Berberis vulgaris* and *Berberis croatica* [9]. It has been shown that BER has antiprotozoal, antimicrobial, and anti-inflammatory properties and traditionally, BER-containing plants have been considered a remedy for dysentery, diarrhea, stomatitis, and hepatitis [10-13]. For several decades, BER has been used in China as an OTC medicine to treat diarrhea [14]. Also, modern pharmacology has shown tumor-suppressing and apoptosis-inducing effects of BER, which make it a potential anti-cancer chemical [15, 16]. The pharmacokinetic profile of BER shows that the oral bioavailability of this compound is very low (< 1%) [17]. Nevertheless, BER may have marked effects on the brain and CNS as it can cross blood-brain-barrier [18].

Furthermore, BER has exerted anti-inflammatory activities in various human and animal tissues such as the liver, adipose tissue, vascular endothelial cells, and intestine [19-22]. Mechanistically speaking, BER diminishes the expression of genes producing cytokines involved in inflammatory pathways (e.g. tumor necrosis factor-α (TNF-α), interleukins, prostaglandins, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS)) via interfering with AMP-activated protein kinase [23].

Considering PTX-induced peripheral neuropathy which is a major concern of its use, and based on the reports on the anti-inflammatory activities of BER, we were encouraged to examine the effect of BER on PTX-induced neuropathy.

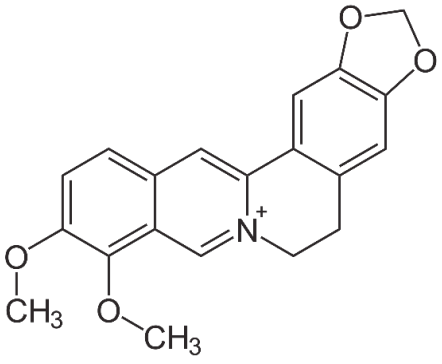

Figure 1 Chemical structure of BER.

2. Materials and Methods

2.1. Drugs and Chemicals

Paclitaxel was obtained from Aboureihan Pharmaceutical Co (Iran) and BER chloride was purchased from Sigma-Aldrich (Germany).

2.2. Animals and grouping

This study was done in 42 male albino mice (30-35 g and 4 weeks old) obtained from Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran. Animals were kept in Plexiglass cages (n = 7) at 22 ± 2°C with 12 hr:12 hr light/dark cycle and they had free access to food and water, ad libitum. Animals were randomly divided into 6 groups (n = 7) as follows: Sham-operated group (mice that received intraperitoneal injections of normal saline instead of PTX), saline-treated group (PTX-treated mice that received normal saline and served as negative control) and BER groups (PTX-treated mice that received BER 5, 10, and 20 mg/kg) as well as imipramine 10 mg/kg (PTX-treated mice that received imipramine and served as positive control). All animal experiments were done in accordance with the National Ethical Guidelines for use and care of laboratory animals.

2.3. Administration of PTX and BER

Based on previous studies [24, 25], a cumulative dose of 8 mg/kg was administered (PTX 2 mg/kg was administered on days 1, 3, 5 and 7) to mice. Also, a single dose of BER 5, 10, and 20 mg/kg was intraperitoneally injected on day 7. Doses and route chosen for BER administration were chosen based on previously published reports [26, 27].

2.4. Hot-plate test

On day 7, animals were placed on a hot-plate apparatus (Ugo Basile 35100, United Kingdom). In order to measure the pain, time to licking, lifting paws or jumping from the hot-plate surface (cut-off time was set at 45 sec) was regarded as the end-points for assessment of response to heat latency. Latencies were measured at 30, 60, 90 and 120 min after BER injection.

2.5. Statistical Analysis

One-way analysis of variance (ANOVA) was used for data analysis and Newman-Keuls test was used to check differences between negative control and other groups. A $P < 0.05$ was considered statistically significant.

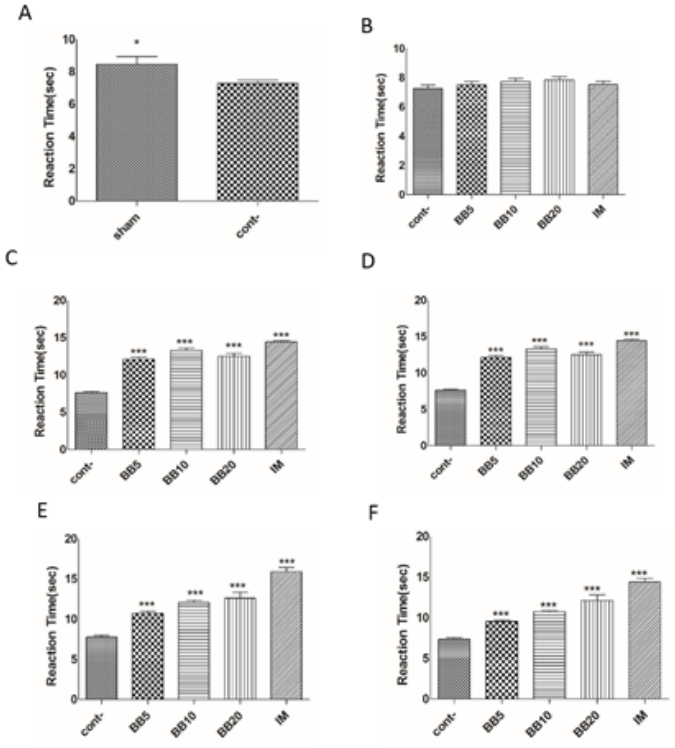

Figure 2 Effects of berberine (BER) on paclitaxel-induced neuropathic pain in mice. Latency to latency to heat was recorded at 0 (2B), 30 (2C), 60 (2D), 90 (2E) and 120(2F) min following treatment with B ER (*P < 0.05 and ***P < 0.001 represent significant differences compared to the negative control). Cont: negative control; BB: Berberine; and IM: Imipramine.

3. Results

3.1. Anti-neuropathic effects of BER measured by hot plate test

As shown in Figure 2A, administration of four doses of PTX (2 mg/kg/day; i.p.) could induce hyperalgesia. As Figure 2B depicts, at time point 0 (i.e. 0 min after BER injection), there were no significant differences between control and BER-treated mice. At time-point 30, significant differences were observed between control and BER-treated groups (Figure 2C). Besides, differences were significant between control and BER 5 and 10 mg at time-point 60 (Figure 2D). At time-points 90 and 120 (Figures 2E and 2F, respectively) also significant differences were observed between control and treatment groups. Altogether, except for time-point 0, at the other time-points, significant differences (P < 0.001) were shown between negative control and BER-treated groups.

4. Discussion

PTX was originally isolated form the bark of pacific yew tree, Taxus brevifolia and is used to treat solid tumor via inducing cell mitosis arrest [28]. However, several adverse reactions such as myelosuppression, kidney damage and peripheral neurotoxicity have been reported for PTX [29]. Neuropathy which is characterized by hyperalgesia, allodynia, numbness, tingling, burning sensations confines PTX application and does not resolve even with cessation of PTX administration [29]. In spite of many studies on PTX-induced neuropathy, no cure has been proposed so far [29].

The results of the current study revealed that four doses of 2 mg/kg/day of PTX could induce neuropathic pain in mice and BER could significantly ameliorate it. Furthermore, a single dose of BER mitigated acute neuropathic pain produced by PTX in mice. BER is a benzylisoquinoline alkaloid found in theroot, rhizome and stem bark of numerous medicinal plants including Hydrastis canadensis, Coptis chinensis, Berberis aquifolium and Berberis vulgaris [30, 31]. BER has been investigated for its anti-hypertensive, antiarrhythmic, antihyperglycemic, anticancer, antidepressant, anxiolytic, neuroprotective, antioxidant, anti-inflammatory, analgesic and hyperlipidemic activities [31-36]. Many clinical studies have well confirmed antioxidant effects of BER in diabetes, high cholesterol, and various inflammatory conditions such as Alzheimer's and cerebral ischemia [30, 33, 34].

PTX-induced neuropathy has been mostly attributed to ROS over-production and decrement of endogenous antioxidants [37]. As a natural alkaloid, BER shows antioxidant

effects and it was found effective for treatment of diabetes, hyperlipidemia, and inflammation [26]. It has been cleared that inflammation and activation of mast cells are involved in neuropathic pain regardless of its cause [29] . BER is one of the strongest antioxidant that can reduce ROS production [31]. In a study, it was shown that quercetin, a polyphenolic flavonoid, could alleviate neuropathic pain by decreasing activation of mast cells. Also, many studies have confirmed anti-inflammatory effects of BER and showed that this effect might contribute to neuropathic pain- relieving properties of BER [38-40].

One of the most active oxidative component that is involved in neuropathy and is induced in diabetic animals, is 2,2-diphenyl-1-picrylhydrazyl (DPPH) [41]. In a study done by Shirwaikar et al, BER reduced DPPH levels in an animal model showing that BER anti-neuropathic effects are induced via different pathways [42].

Furthermore, BER can inhibit neurodegeneration via ROS, MAO (monoamine oxidases) and AchE (acetylcholinesterase) inhibition and GLP-1, Nrf2, Akt-PI3K, CREB and pCREB activation [43]. The aforementioned mechanisms have been investigated to develop new approaches for treatment of Alzheimer's, Parkinson's and other neurodegenerative diseases [43].

BER posed neuroprotective effects by activation of Akt-Pi3 pathways in neuronal cell lines, decreased NF-kB inflammatory effects in neuronal cell lines and alleviated neuropathy in animal models [43]. Furthermore, short-term administration of BER in acute stroke posed protective effects and this confirmed that beside the effect of long-term administration of BER, short-term usage of this compounds is also of considerable importance [43].

5. Conclusion

Altogether, our results showed that PTX could induce neuropathic pain as reflected by hyperalgesia and a single dose of BER could alleviate PTX-induced thermal hyperalgesia. As a limitation, the present study lacked mechanistic investigations, therefore, future studies should clarify the role of ROS-scavenging or antihistaminic effects of BER in its anti-neuropathic properties.

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Conflict of interest

The authors declare no conflict of interest.

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