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Effect of curcumin on diabetic peripheral neuropathic pain: Possible involvement of opioid system

Hamid R Banafshe [a,c,*], Gholam A. Hamidi [b], Mahdi Noureddini [b], Seyyed Mehdi Mirhashemi [d], Rasool Mokhtari [a,b], Mehdi Shoferpour [a]

[a] Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan 87159-88141, Iran
[b] Physiology Research Center, Kashan University of Medical Sciences, Kashan 87159-88141, Iran
[c] Department of Addiction studies, School of Medicine, Kashan University of Medical Sciences, Kashan 87159-88141, Iran
[d] Research Center for Biochemistry and Nutrition in Metabolic Disorder, School of Medicine, Kashan University of Medical Sciences, Kashan 87159-88141, Iran

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ABSTRACT

Neuropathic pain is one of the most common complications of diabetes mellitus. As efficacy and tolerability of current therapy for neuropathic pain are not ideal, we need to develop the novel drug for better treatment. Curcumin as a natural flavonoid from Curcuma longa has considerable effects on nervous system such as, antidepressant, antinociceptive and neuroprotective effects. The present study was designed to investigate the effect of curcumin on diabetic peripheral neuropathic pain and possible involvement of opioid system. A single dose of 60 mg/kg streptozotocin was injected intraperitoneally to induce diabetes in rats. STZ-induced diabetic rats were treated with curcumin (50 mg/kg/day) acute and chronically. Thermal hyperalgesia and mechanical allodynia were measured on the days 0, 7, 14 and 21 after diabetes induction as behavioral scores of neuropathic pain. Chronic, but not acute, treatment with curcumin prevents the weight loss and attenuates mechanical allodynia in STZ-induced diabetic rats. Pretreatment with naloxone (1 mg/kg) significantly reduced anti-allodynic effect of chronic curcumin in von Frey filament test. Our results suggest that curcumin can be considered as a new therapeutic potential for the treatment of diabetic neuropathic pain and the activation of opioid system may be involved in the antinociceptive effect of curcumin.

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1. Introduction

Neuropathic pain is one of the most common complications of diabetes mellitus. Diabetic peripheral neuropathic pain involves the deep muscular aches, lancinating pains and a persistent burning or tingling sensation, usually in the legs and feet. Patients with diabetic peripheral neuropathic pain may also experience allodynia and hyperalgesia (Ziegler, 2008). As efficacy and tolerability of current therapy for Diabetic neuropathic pain are not ideal, we need to develop the novel drug for better treatment of this chronic disease (Spallone et al., 2012). Curcumin, a natural flavonoid from Curcuma longa, is a major component of turmeric and exhibits a wide range of therapeutic effects such as anticarcinogenic, antioxidant, antimicrobial and neuroprotective properties (Lopresti et al., 2012). Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at high dose ranges without any toxic effects. Thus, both turmeric and curcumin have potential in the development of modern medicine for treatment of various diseases (Park et al., 2012). It is well known that curcumin decreases the inflammatory responses through inhibition of cyclooxygenase 2, lipoxygenase 5 and nitric oxide synthase (Zhou et al., 2011). In addition, the antinociceptive effects of curcumin have been demonstrated in different pain models such as orofacial and inflammatory pain (Mittal et al., 2009; Park et al., 2012). Recently, it was also shown that curcumin exerts anti-hyperalgesic effects in a mouse model of neuropathic pain (Zhao et al., 2012). The antinociceptive mechanisms of curcumin have not been well understood. A few studies suggest the role of delta and mu-opioid receptors in antinociceptive effect of curcumin (Tajik et al., 2007; Zhao et al., 2012). Taken together the present study was designed to investigate the effect of curcumin on diabetic peripheral neuropathic pain and possible involvement of opioid system in this effect.

2. Material and methods

2.1. Animals

Experiments were carried out on Male albino Wistar rats (Pasteur's institute, Tehran, Iran) weighing 220–280 g. Three to

* Corresponding authors at: Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Ravand Street, 87159-88141, Kashan. Iran. Tel.: +98 361 5550021; fax: +98 361 5551112.
E-mail address: banafshe57@hotmail.com (H.R Banafshe).

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four rats were housed in a cage under a 12 h light/dark cycle with food and water available ad libitum. Procedures involving animals and their care were conducted in conformity with National Institutes of Health guidelines for the care and use of laboratory animals.

2.2. Drugs and reagents

Streptozotocin, curcumin and naloxone were purchased from Sigma (St Louis, MO, USA).Glucose oxidase peroxidase kit was purchased from Zistchimie Company (Tehran, Iran).

2.3. Induction and assessment of diabetes

A single dose of 60 mg/kg streptozotocin freshly dissolved in ice-cold 0.1 M citrate buffer (pH 4.5) was injected intraperitoneally (i.p.) to induce diabetes. The age-matched normal animals that received an injection of an equivalent volume of citrate buffer comprised a non-diabetic control group. Diabetes was confirmed 72 h after streptozotocin injection, the blood samples were collected through the tail vein and fasting plasma glucose levels were measured using glucose oxidation method (Zistchimie, Tehran). Only those animals with a serum glucose level higher than 250 mg/dl were selected as diabetic. During the next weeks, diabetes was also reconfirmed by the presence of polyphagia, polydipsia, polyuria and weight loss (Fox et al., 1999).

2.4. Drug treatment

After a basal assessment of neuropathic pain at 7th day of diabetes induction, animals were randomly selected and divided in six groups ($n=10$/group). First group consists of a non-diabetic control animals, second group is the diabetic control and third and fourth group consisted of diabetic animals treated with curcumin (50 mg/kg/day, i.p.) acute and chronically. In acute treatment, single dose of curcumin administered only 30 min prior to the pain assessment and in chronic treatment, curcumin starting from 7th day till 21st day injected once a day (Mittal et al., 2009). The control groups received the vehicle of curcumin and other diabetic groups received i.p. injection of curcumin at doses 50 mg/kg. Curcumin was freshly suspended in 25% dimethyl sulphoxide (DMSO) with a few drops of chromophore. In fifth and sixth group, we injected naloxone (1 mg/kg i.p.) 30 min before curcumin administration (Banafshe et al., 2012).

2.5. Behavioral tests of neuropathic pain

Hyperalgesia to noxious thermal stimulus and allodynia to mechanical stimuli were determined as behavioral score of neuropathic pain by using the radiant heat plantar and von Frey test, respectively. These tests were performed during the day portion of the circadian cycle (09:00–16:00 h). After cage exploration and major grooming activities ceased, we made the behavioral tests. The behavioral scores of neuropathic pain, body weight and plasma glucose levels were also measured before the experiment and 7, 14 and 21 day after the diabetes induction (Verdi et al., 2013).

2.5.1. Plantar test

Thermal hyperalgesia was assessed as previously reported (Hamidi et al., 2012). Paw withdrawal latency in response to radiant heat was measured by using plantar test apparatus (Ugo Basile, Varese, Italy). Rats were placed within a Plexiglass enclosure (but not restrained) on a transparent glass floor. An infrared beam that constitutes the heat source was moved beneath the mid-plantar surface of the hind paw. Thermal withdrawal latency was defined as the latency (seconds) between the heat stimulus onset and paw withdrawal using a feedback-controlled shut-down unit. A cut-off time of 22 s was used to avoid tissue damage. Each paw was tested three times alternatively at minimum intervals of 5 min between stimulation to avoid sensitization. The mean latency of the withdrawal responses was considered as hyperalgesia score.

2.5.2. Von Frey filament stimulation

Mechanical allodynia was quantified by measuring the hind paw withdrawal response to von Frey filament. We studied the effect of von Frey filament stimulation with bending forces ranging from 2 to 60 g, (Stolting Inc., Wood Dale, IL). Rats were placed on a mesh floor, covered by an inverted transparent plastic box ($18\times18\times25$ cm) and allowed to adapt for approximately 15 min, or until exploratory behavior ceased. A series of von Frey filament stimuli were delivered in an ascending order of forces to the central region of the plantar surface of the hind paw. The stimulation was applied until the rat withdrew its paw or the fiber bowed. Lifting of the paw due to normal locomotor behavior was ignored. The smallest filament size which evoked at least two withdrawal responses during three consecutive applications was considered as withdrawal threshold (Chaplan et al., 1994; Banafshe et al., 2012).

2.6. Statistical analysis

All data are presented as Mean ± S.E.M. and differences are considered significant if the P value was less than 0.05. Values for behavioral response were analyzed using analysis of variance (ANOVA) with repeated measures followed by Tukey's honest squares difference (HSD) test. Group was considered as the between-subjects and day as within-subjects.

3. Results

3.1. Effects of treatment on blood glucose and body weight

Streptozotocin (STZ) injection induced a significant increase in plasma glucose levels in comparison with control animal. Treatment with curcumin did not reduce hyperglycemia in diabetic rats significantly (Fig. 1). As shown in Fig. 2, there was a significant decrease in the body weight of diabetic rats as compared with aged matched control animals ($F_{3,35}=72.1$, $P<0.001$). Chronic

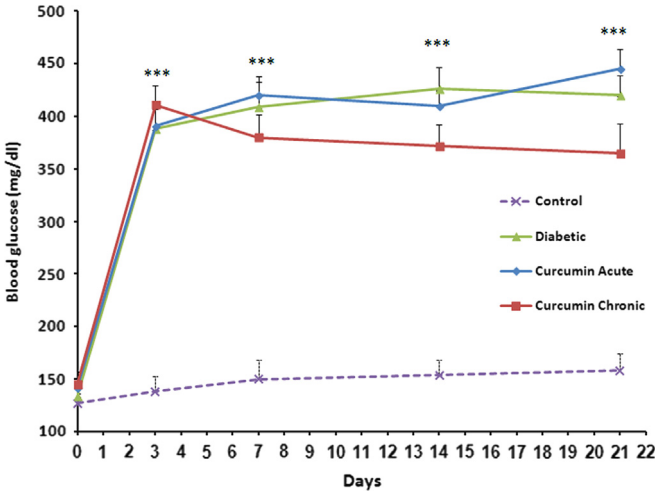

Fig. 1. The effects of streptozotocin (STZ) and curcumin treatment on blood glucose levels. The blood glucose concentration was measured prior to STZ injection (day 0) and different days post-STZ injection. The results are expressed as Mean ± S.E.M. ($n=8$–10/group). ***$P<0.001$ versus control group.

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