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Querectin improves myelin repair of optic chiasm in lyolecithin-induced focal demyelination model

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A R T I C L E I N F O

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A B S T R A C T

Although the beneficial effects of quercetin on oligodendrocyte precursor cell (OPCs) population has been evaluated *in-vitro,* there are few studies about the effects of quercetin on myelin repair in the context of demyelination. The aim of this study was to investigate the effects of querectin on functional recovery and myelin repair of optic chiasm in lysolecithin (LPC)-induced demyelination model. Demyelination was induced by local injection of LPC 1% (2 µl) into rat optic chiasm. Querectin at doses 25 or 50 mg/kg was administrated daily by oral gavage for 7 or 14 days post LPC. Visual evoked potential (VEPs) recordings were used to assess the functional property of the optic pathway. Immunostaining and myelin staining were performed on brain sections 7 or 14 days post lesion. Electrophysiological data indicated that LPC injection increased the latency of VEPs waves and quercetin effectively reduced the delay of visual signals. The level of glial activation was alleviated in animals under treatment of quercetin compared to vehicle group. Furthermore, quercetin treatment decreased the extent of demyelination areas and increased the remyelination process following LPC injection. Overall, our findings indicate that quercetin could remarkably improve the functional recovery of the optic pathway by its protective effects on myelin sheath and attenuation of glial activation.

1. Introduction

Oligodendrocytes are responsible for myelin formation in the central nervous system (CNS) [1]. Destruction of oligodendrocytes and myelin loss are considered as the most common hallmarks of several neurodegenerative disorders, such as multiple sclerosis (MS) [2]. MS is a chronic inflammatory disease of CNS which is mainly characterized by oligodendrocyte death, myelin damage, and disturbance of action potential conduction [3]. Furthermore, visual disturbance occurs in more than 70% of MS patients [4]. However, endogenous remyelination routinely occurs in MS, but recruitment and differentiation of oligodendrocyte precursor cells (OPCs) often fail following progression of MS disease [5]. Therefore, therapeutic approaches which lead to OPCs protection and promote the migration and differentiation of endogenous OPCs in the area of damage have been regarded as the ideal strategy for treating MS [6]. Recently, the application of natural products which possessing lower side effects compared to the available chemical drugs has emerged as a novel therapeutic approach in regenerative medicine. Quercetin is regarded as one of the most abundant natural flavonoids which is present in several vegetables and fruits [7]. Quercetin possesses a wide range of pharmacological functions, including anti-tumor effects [8], anti-oxidant [9] and antiviral activities [10]. In addition, it has been shown that quercetin significantly reduces Aβ (1-42)-induced cytotoxicity in primary neurons [11]. Quercetin also attenuates neuronal cell death in ischemia animal model [12].The anti-inflammatory effect of quercetin has been well documented both *in-vitro* and *in-vivo* [13,14]. Quercetin administration reduces the production of inflammatory factors [15] and decreases glial scar formation

Abbreviations: CNS, central nervous system; MS, multiple sclerosis; OPCs, oligodendrocyte precursor cells; OGD, oxygen/glucose deprivation; EAE, experimental autoimmune encephalomyelitis; VEP, visual evoked potential; LPC, lysolecithin; i.p, intraperitoneal; qRT-PCR, qantitative real time polymerase chain reaction; PBS, phosphate buffer saline; PFA, paraformaldehyde; DAPI, 4′, 6-diamidino-2-phenylindole; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium-binding adapter molecule; PHI, perinatal hypoxia ischemia

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[16]. Furthermore, several lines of evidence showed the protective effects of quercetin on OPCs population. It has been shown that quercetin application attenuates the apoptosis of cultured OPCs and increases the OPCs proliferation in oxygen/glucose deprivation (OGD) injury model [17,18]. Another study demonstrated that quercetin administration through enhancement of OPCs proliferation and oligodendrocytes survival remarkably improved cognition performance and myelination in cerebral hypoxia-ischemia induced brain injury model [19]. Furthermore, quercetin ameliorates the severity of experimental autoimmune encephalomyelitis (EAE) model of MS by blocking IL-12 production [20]. The local injection of lysolecithin (LPC) into the optic chiasm has been introduced as a useful model to examine demyelination and remyelination processes in the CNS [21]. Visual evoked potential (VEP) recording has been developed as a sensitive and reliable tool for diagnosing demyelination in both MS patients and experimental model of demyelination [22]. The present study was designed to examine whether quercetin administration could improve the functional recovery of optic chiasm in LPC-induced demyelination model. Moreover, the impact of querectin treatment on glial activation and myelin repair of optic chiasm was evaluated in the context of demyelination.

2. Materials and methods

2.1. Drugs

Quercetin and lysolecithin (LPC) were purchased from Sigma-Aldrich (St.Louis, USA). Quercetin and LPC were dissolved in sterile saline containing 0.1% Tween-80 [19] and sterile saline, respectively. Quercetin doses were selected on the basis of previous report by Braun et al. [23].

2.2. Animals

All experimental procedures were carried out on adult male Wistar rats (Animal house of Babol University of Medical Sciences, Babol, Iran), weighing 220–250 g. Animals were kept under a 12 h light/dark cycle with free access to food and water. All experimental protocols were approved by the local ethical committee of Babol University of Medical Sciences, which was in accordance with the international guidelines on the use of laboratory animals. Forty-eight rats were included in this study, each group containing six.

2.3. Lysolecithin microinjection and visual evoked potential recording

LPC injections were performed based on our previous report [4]. Briefly, animals were anesthetized with intraperitoneal (i.p) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and placed in a stereotaxic instrument (Stoelting, USA). Two microliters of LPC 1% was injected into the optic chiasm with the following coordinates:

(AP: 0 mm, ML: 0 mm from bregma, DV: −7.3 mm from the dura surface)

VEPs recording was described in our previous report [4]. Briefly, two monopolar electrodes, one recording and one reference, were implanted on the occipital cortex (AP: −7 mm, ML: −3 mm from bregma) and frontal lobe (AP: +2 mm, ML: +1.5 mm), respectively. Light stimulation was carried out using a general evoked response stimulator (D3111 Data Acquisition, Science Beam Co., Tehran, Iran) at 0.5 Hz frequency and for 400 repetitions. Recorded signals were amplified at a gain of 1000 and eprobe software was used for data analysis. For VEPs signal analysis, the latency between flash light and the first positive wave was measured on days 0, 7 and 14 post LPC injection.

2.4. Experimental procedures

Forty-eight rats were randomly assigned to 8 experimental groups as follows: Groups 1-2: saline + saline, which received 2 μl sterile saline as LPC vehicle into the optic chiasm and then sterile saline solution containing 0.1% Tween-80 as quercetin solvent was administrated by gavage for 1 or 2 weeks post LPC injection; Groups 3-4: LPC + saline, a single LPC 1% (2 μl) shot was injected into the optic chiasm in these groups and then sterile saline solution containing 0.1% Tween-80 was administrated orally for 1 or 2 weeks after LPC injection; Groups 5-8: LPC + quercetin, in these experimental groups, focal demyelination was induced by LPC injection and then animals were treated by oral administration of quercetin at 25 or 50 mg/kg doses for 1 or 2 weeks post lesion. The administration of vehicle or quercetin began 4 h after the surgical procedure and oral gavages of drugs were continued until the end of experiments.

VEPs were recorded before LPC injection and also on days 7 and 14 post injection. After electrophysiological recordings, optic chiasm tissue was collected based on the appropriate time point and the effect of quercetin administration on glial activation and myelin repair was examined using immunostaining.

2.5. Immunostaining

Immunostaining was performed based on our previous report [24]. Briefly, animals were deeply anesthetized and transcardially perfused by phosphate buffered saline (PBS) and 4% paraformaldehyde (PFA) solutions. Brain tissues were removed and post-fixed in PFA for 12–16 h. Tissue samples were immersed in 30% sucrose for 48 h. Coronal sections (6 μm thickness) were prepared by cryostat instrument (MICROM HM 525, Thermo Scientific) from the optic chiasm. Tissue sections were washed with PBS. Non-specific bindings were blocked using 10% normal goat serum and 0.3% Triton X-100 in PBS for 1h. Sections were incubated with primary antibodies including rabbit anti-GFAP (1:400, Z0334, Dako), rabbit anti-PLP (1:100, ab28468, Abcam inc.) or rabbit anti-Iba1 (1:500, 019-19741, Wako) overnight at 4 °C. After washing with PBS, the appropriate secondary antibody (Goat anti-rabbit Alexa Fluor®594, 1:1000, ab150116, Abcam inc.) was added for 1 h at room temperature. Tissue sections were washed with PBS and nuclear staining was done by 4´,6-diamidino-2-phenylindole (DAPI). Tissue sections were evaluated under fluorescence IX71 microscope (Olympus, Japan) and images from optic chiasm were taken using DP-27 camera. Histological data quantification was done using Image J software (version 1.42 V, NIH, USA) as we have described previously [4,24,25]. Three sections from each slide, 3 slides from each animal, and 3 rats were used for each group.

2.6. Fluoromyelin staining

Fluoromyelin staining was performed according to the manufacturer's protocol (FluoroMyelin™ Green Fluorescent Myelin Stain, F34651, Invitrogen). Tissue sections were washed with PBS and then fluoromyelin stain was added for 20 min. Sections were washed with PBS and the extent of demyelination area was examined under fluorescence microscope (Olympus, Japan). In every section, the extent of demyelination areas in optic chiasm were assessed using Image J software (version 1.42 V, NIH, USA) as the percentage of total area as previously described by Mozafari et al., [26]. The extent of demyelination was averaged for 9 sections from each animal (n = 3 rats for each experimental group). Therefore, 27 sections were used for histological analysis.

2.7. Statistical analysis

Electrophysiological data was analyzed using two-way ANOVA, followed by Bonferroni *post-hoc* test. Histological results were assessed by one-way ANOVA, followed by Tukey *post-hoc* test. The results are expressed as mean ± SEM and p values < 0.05 has been considered statistically significant.

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