Cytokine 110 (2018) 78–86

Contents lists available at ScienceDirect

Cytokine

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

Imperatorin ameliorates lipopolysaccharide induced memory deficit by mitigating proinflammatory cytokines, oxidative stress and modulating brain-derived neurotropic factor

Amrita A. Chowdhury[a], Nitin B. Gawali[a], Prashant Shinde[b], Renuka Munshi[c], Archana R. Juvekar[a,*]

[a] Pharmacology Lab, Department of Pharmaceutical Sciences and Technology (DPST), Institute of Chemical Technology (ICT), N. P. Marg, Matunga (E), Mumbai 400019, India
[b] Medicinal and Natural Product Research Laboratory, Department of Pharmaceutical Sciences and Technology (DPST), Institute of Chemical Technology (ICT), N. P. Marg, Matunga (E), Mumbai 400019, India
[c] Department of Clinical Pharmacology, B. Y. L. Nair Charitable Hospital and Topiwala National Medical College, Dr. A. L. Nair Road, Mumbai 400008, India

ARTICLE INFO

Keywords:
Brain derived neurotrophic factor
Proinflammatory cytokines
Imperatorin
Lipopolysaccharide
Neuroinflammation

ABSTRACT

Background: Lipopolysaccharide (LPS), an endotoxin from the outer membrane of Gram negative bacteria has been reported to cause neuroinflammation and learning and memory deficits. There are reports describing the beneficial effects of Imperatorin (IMP), a naturally occurring furanocoumarin in central nervous system (CNS) disorders such as anxiety and epilepsy.
Objective: In the current study, we investigated whether IMP protects against LPS mediated memory deficits and neuroinflammation.
Methods: Mice pretreated with IMP (5, 10 mg/kg *po*) were administered LPS (250 μg/kg *ip*) for 7 days. Memory was evaluated in the Morris water maze (MWM) and Y maze. The mice were euthanised and different biochemical assessments were carried out to measure oxidative stress and acetyl choline esterase (AChE). Further, evaluation of proinflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) levels and brain derived neurotrophic factor (BDNF) in hippocampus and cortex of brain were performed.
Results: LPS administration caused poor memory retention in both, MWM and Y maze, and caused distinct oxidative stress since decrease in superoxide dismutase (SOD), reduced glutathione (GSH) levels and increased lipid peroxidation were observed. Also, a significant rise was observed in the levels of AChE. Moreover, a rise in TNF-α and IL-6 levels and depleted levels of BDNF were noted. IMP pretreatment reversed LPS induced behavioral and memory disturbances and significantly decreased the oxidative stress and AChE levels. It also reduced TNF-α and IL-6 levels and caused a significant upregulation of BDNF levels.
Conclusion: Present study highlights the potential neuroprotective role of IMP against LPS mediated cognitive impairment and neuroinflammation.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and is regarded as the principal cause of dementia in the elderly population. The hallmarks of AD include progressive accumulation of amyloid (Aβ) plaques outside neurons and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein within neuronal cells. These eventually lead to disruption of synaptic transmission and neuronal loss [1]. Currently, the World Alzheimer report 2015 states that the prevalence of AD is an estimated 46.8 million cases and

Abbreviations: Aβ, amyloid beta; AChE, acetyl cholinesterase; AD, Alzheimer's disease; ANOVA, analysis of variance; BSA, Bovine serum albumin; BDNF, brain derived neurotrophic factor; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals; CNS, central nervous system; DNP, donepezil; LPS, lipopolysaccharide; GSH, reduced glutathione; IL-6, interleukin-6; IL-10, interleukin-10; IMP, imperatorin; MDA, malonaldehyde; MWM, morris water maze; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NFTs, neurofibrillary tangles; PBS, phosphate buffer saline; ROS, reactive oxygen species; SAB, spontaneous alteration behavior; SOD, superoxide dismutase; SEM, standard error of the mean; TNF-α, tumor necrosis factor alpha

* Corresponding author.
E-mail address: juvekar.archana@gmail.com (A.R. Juvekar).

https://doi.org/10.1016/j.cyto.2018.04.018
Received 24 October 2017; Received in revised form 21 March 2018; Accepted 16 April 2018
1043-4666/ © 2018 Elsevier Ltd. All rights reserved.

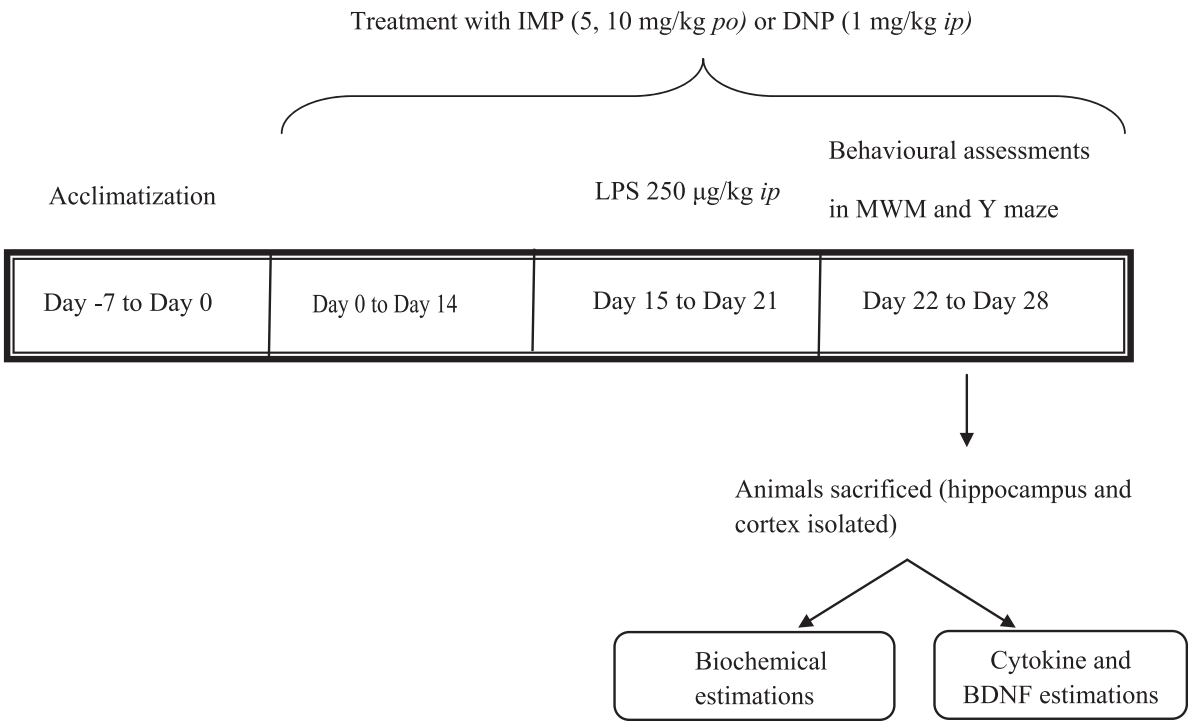

Fig. 1. Diagram portraying treatment schedule. Saline, IMP and DNP pretreatment were carried out for 14 days. From day 15 to day 21 onwards, LPS (250 µg/kg *ip*) was injected. From day 22 to day 27, behavioral evaluations were carried out in MWM and Y-maze. Post behavioural evaluation, the mice were sacrificed and the biochemical and cytokine estimations were carried out.

predicts that by 2030, there will be an estimated 74.7 million cases of AD whereas in 2050, the estimated number of AD patients will rise up to 131.5 million [2].

Recently, many studies have pointed out about the role of neuroinflammation in AD [3,4]. Neuroinflammation was initially speculated to occur only in the late to end stages of the disease, as a response to neuropathological changes occurring in the AD brain. However, recent preclinical, genetic and bioinformatic studies have revealed that immune system stimulation occurs early on in AD and plays a key role in the disease pathogenesis [5,6]. Microglial activation, dysfunctional microglial clearance of Aβ plaques [7], excessive production and release of chemokines and cytokines at the location of Aβ plaques, activation of the complement system, all play a key role in exacerbating AD pathology [8].

Several researchers indicate that LPS administration, a bacterial endotoxin, obtained from outer membrane of gram negative bacteria causes memory impairment [9,10,11] and neuroinflammation in experimental animals that resemble AD like cognitive decline and pathology [11,12,13]. Further in support of such studies, Lee et al reported that LPS administration causes increased amyoidogenesis due to enhanced β and γ-secretase activities [14]. Moreover, LPS administration also promoted tau hyperphosphorylation [15].

IMP is a naturally occurring linear furanocoumarin, isolated from fruits of *Angelica dahurica* and *Angelica archangelica* [16]. IMP has been reported to have a multitude of pharmacological activities such as anticancer, antihypertensive [17], antiviral [18] and anti-inflammatory [19] effects. Many researchers have reported about the neuromodulatory effects of IMP. Luszczki et al demonstrated the anticonvulsant action of IMP in an electroshock seizure model [16] and also reported that it potentiates the anticonvulsant activity of classical antiepileptic drugs [20]. Moreover, IMP has been reported to possess memory enhancing [21,22] and anxiolytic activity [23]. Some researchers have also demonstrated that IMP can suppress voltage gated sodium channels [24] and calcium channels [25].Taking into consideration, the beneficial effects of IMP on inflammation and neuromodulation, we thought that it is worthwhile to explore the role of IMP in LPS mediated cognitive impairment and neuroinflammation, which has not been studied yet.

2. Materials and methods

2.1. Drugs and treatment schedule

IMP was extracted from the fruits of *Aegle Marmelos (Linn) Correa* as per the method described by Shinde and Laddha [26]. LPS from Escherichia coli serotype 0111:B5 was purchased from Sigma Aldrich Co Ltd. Dr. Reddy's Laboratories Ltd; Hyderabad, India offered donepezil hydrochloride (DNP) as a gift sample. ELISA kits of mouse BDNF, TNF-α and IL-6 were procured from Krishgen BioSystems. All the other chemicals were of analytical grade. IMP was dissolved in 0.5% sodium CMC for oral *(po)* administration and DNP and LPS were dissolved in saline for intraperitoneal (*ip*) administration. Drug solutions were made fresh each day during the experiment. Thirty animals were used for the study after being randomized into five groups, each group consisting of 6 animals. The mice were administered the drugs for 14 days after which 250 µg/kg of LPS was concomitantly administered via the *ip* route for the next 7 days. The drug administration was continued till the mice were sacrificed on day 28. The dose of IMP was chosen by review of earlier literature where IMP was reported to have nootropic activity [22]. The dosing schedule was as follows:

Group I: Vehicle Control (0.3 ml saline)
Group II: Saline (0.3 ml) + LPS (250 µg/kg *ip*)
Group III: IMP (5 mg/kg) + LPS (250 µg/kg *ip*)
Group IV: IMP (10 mg/kg) + LPS (250 µg/kg *ip*)
Group V: DNP (1 mg/kg) + LPS (250 µg/kg *ip*)

The outline of the treatment schedule and behavioral test is shown in Fig. 1.

Download English Version:

https://daneshyari.com/en/article/8628748

Download Persian Version:

https://daneshyari.com/article/8628748

Daneshyari.com