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Other work


• Manoja Kumar Brahma, Preeti Dohare, Saurabh Varma, Puja Garg, Prasanta Kumar Biswal, Piyali Dhar Chowdhury, C.Nath and Madhur Ray. The effect of monensin and tetrodotoxin on the neuronal apoptotic death in global cerebral ischemia in gerbil (communicated).


Patent filed

Indian

No INF/PAT/03/2006 S-005-095 to S-005-101; S-005-181 to S-005-018; S-005-645 to S-005-664 to S-005-667 “Neurocerebrovascular disorders” Atul Goel, Fateh Veer Sing, Puja Garg, Preeti Dohare & Madhur Ray

International (to be filed)

Curcuma oil modulates the nitric oxide system response to cerebral ischemia/reperfusion injury

Preeti Dohare a, Saurabh Varma b, Madhur Ray a,**

a Division of Pharmacology, Central Drug Research Institute, P.O. Box No. 173, Chatter Manzil Palace, Lucknow, UP 226001, India
b Institute of Pathology, Indian Council of Medical Research, N. Delhi, India

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ABSTRACT

The antioxidant activity of COoil in cerebral stroke has been reported earlier. We have attempted here to clarify the mechanisms underlying the neuroprotection against experimental cerebral ischemia by Curcuma oil (COoil), isolated from the rhizomes of Curcuma longa. COoil (250 mg/kg i.p.) was given 30 min before focal ischemia in rats caused by occlusion of the middle cerebral artery (1 h of occlusion, 24 h of reflow). Ischemia, leads to elevation in [Ca2+] this sets into motion a cascade of ischemic injury which was attenuated by COoil. COoil reduced post-ischemic brain neutrophil infiltration in the ischemic area, controlled tissue NOx levels and the neuronal levels of nitric oxide, peroxynitrite and reactive oxygen species when measured after 24 h of reflow. Double immunofluorescence staining analysis and Western immunoblot analysis with COoil treatment showed that the expression of nitric oxide synthase (NOS) isoforms were decreased significantly compared to the untreated ischemia group. Ischemia is associated with increased in TUNEL (TdT-mediated dUTP nick-end labeling) positive cells in brain sections indicating DNA fragmentation. The COoil treated group showed a significant decrease in numbers of apoptotic cells compared to the untreated ischemia group, as seen in the flowcytometric analysis of the neurons. Results of immunohistochemistry and Western immunoblot indicate that COoil suppressed the elevated protein level of Bax, and aided mitochondrial translocation and activation of bcl-2 by altered mitochondrial membrane potential. It also inhibits the cytosolic release of apoptogenic molecules like cytochrome c, inhibits the activation of caspase-3 and the expression of p53 ultimately inhibiting apoptosis. Our observations suggest that high levels of NO generated by NOS isoforms are partially responsible for exacerbating the neuronal damage induced by MCAo by intraluminal filament.

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Curcuma Oil: Reduces Early Accumulation of Oxidative Product and is Anti-apoptogenic in Transient Focal Ischemia in Rat Brain

Priyanka Rathore · Preeti Dohare · Saurabh Varma · Aparajita Ray · Uma Sharma · N. R. Jaganathanan · Madhur Ray

Abstract Turmeric is a source of numerous aromatic compounds isolated from powdered rhizomes of Curcuma longa Linn. The constituents are present as volatile oil, the Curcuma oil (C.oil), semi-solid oleoresins and non-volatile compounds such as curcumin. A rapidly expanding body of data provides evidence of the anti-cancer action of Curcumin, and most importantly in the present context, its neuroprotective activity. Almost nothing is known about such activity of C.oil. We report that C.oil (500 mg Kg⁻¹ i.p.) 15 min before 2 h middle cerebral artery occlusion (MCAo) followed by 24 h reflow in rats significantly diminished infarct volume, improved neurological deficit and counteracted oxidative stress. The percent ischemic lesion volume on diffusion-weighted imaging was significantly attenuated. Mitochondrial membrane potential, reactive oxygen species, peroxynitrite levels, caspase-3 activities leading to delayed neuronal death were significantly inhibited after treatment with C.oil. These results suggest that the neuroprotective activity of C.oil against cerebral ischemia is associated with its antioxidant activities and further; there is attenuation of delayed neuronal death via a caspase-dependent pathway. C.oil appears to be a promising agent not only for the treatment of cerebral stroke, but also for the treatment of other disorders associated with oxidative stress.

Keywords Curcuma oil · MCAo · Rat · Ischemia · Reperfusion · Antioxidants · SOD · CAT · GSH-Px · Caspase-3 · ROS · Mitochondrial membrane potential · Peroxynitrite · Apoptosis · Necrosis

Introduction

The ancient Indian system of medicine—Ayurveda—is concerned with the prevention, diagnosis and cure of diseases. Ayurveda describes a number of beneficial effects of the rhizomes and leaves of various species belonging to the Zingiberaceae family, especially those of Curcuma longa Linn. (Syn. Curcuma domestica Valeton). The rhizomes of the plants are popularly known as turmeric in English or Haldi in Hindi. C. longa is one of the widely reputed medicinal plants, which are attributed with tonic, rejuvenating, anti-stress, anti-fatigue, anti-oxidant and apoptogenic properties [1]. Turmeric contains essential oils, mostly terpenoids (such as turmerones, atlantones and zingiberene) and flavonoids—the curcuminoids (including curcumin) [2, 3]. Modern interest in turmeric began in the 1970's when researchers found curcumin has neuroprotective properties (especially in amyloid pathology in Alzheimer's disease) anti-carcinogenic, and anti-HIV-1 integrase activities. There are substantial data supporting its anti-inflammatory, anti-tumour, reno-protective, cardioprotective, and lipid-lowering activities [4–7].

However, curcuma oil has not received the attention of scientists and its potential uses in medicine have not been studied extensively. It is only known for its anti-fungal and
Amino acid-based enantiomerically pure 3-substituted 1,4-benzodiazepin-2-ones: A new class of anti-ischemic agents

Jitendra Kumar Mishra, Puja Garg, Preeti Dohare, Ashutosh Kumar, Mohammad Imran Siddiqi, Madhur Ray and Gautam Panda

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, UP, India
Pharmacology Division, Central Drug Research Institute, Lucknow 226001, UP, India
Molecular and Structural Biology Division, Central Drug Research Institute, Lucknow 226001, UP, India

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Abstract—A series of 3-substituted 1,4-benzodiazepin-2-ones derived from S and R amino acids were evaluated for their anti-ischemic activity in vitro. Treatment with compounds 7h, 16, 9d, and 17 decreased the apoptotic neuronal number, however increased the neuronal viability. The compounds decreasing apoptosis could protect neurons from the ischemic injury. The difference in the activities of 1,4-benzodiazepin-2-ones derived from S- and R-amino acids is discussed and explained on the basis of molecular modeling studies.

Keywords: Anti-ischemic agents; 1,4-Benzodiazepin-2-ones; Amino acids.

Brain injury by transient or permanent ischemia afflicts a large number of patients with death or permanent disability. With the onset of ischemia, critical balance between the demand and supply of oxygen and substrates fails, leading to the damage of reversible or irreversible cellular interdependent pathways and it can be managed by timely protection offered by the drugs.

Benzodiazepine derivatives are of considerable interest because of their wide range of biological activities such as anticonvulsant, cholecystokinin receptor A and receptor B antagonists, platelet-activating factor antagonists, GPIIb/IIIa inhibitors, and Ras farnesyltransferase inhibitors. Another well-known member of benzodiazepine family is pyrrolo[2,1-c][1,4]benzodiazepines (PBDs), known for their potential as antitumor agents, gene regulators, and DNA probes. Although diverse biological activities of 1,4-benzodiazepines are known, to the best of our knowledge there is no report on anti-ischemic efficacy of 3-substituted 1,4-benzodiazepin-2-ones (Fig. 1).

Figure 1. Biologically active 1,4-benzodiazepine derivatives.

Toward the objective of finding new anti-ischemic agents, we have synthesized a series of S and R-amino acid-based enantiomerically pure 3-substituted 1,4-benzodiazepin-2-ones (Schemes 1 and 2) and screened for anti-ischemic activity in vitro following the literature methods. Compounds 7a-h, 14, 15, and 16 derived from S-amino acids were evaluated for apoptotic/necrotic quantification of neuronal population in vitro (Fig. 2 and Table 1). Control neurons (LL) showed no FITC/PI-positive staining (0.05%/0.6%). The number of FITC-positive neurons (LR) was increased to 30.22% in ischemic neurons. Compounds 7h and 16 derived from S-methionine and 4-hydroxy-S-proline decreased the number of viable neurons to 9.08% and 3.79%, respectively. The number of viable neurons was also increased by the treatment of compounds. In the ischemic group without treatment,