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Research Report

Curcumin, encapsulated in nano-sized PLGA, down-regulates nuclear factor κB (p65) and subarachnoid hemorrhage induced early brain injury in a rat model

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ABSTRACT

Background: More and more evidence revealed early brain injury (EBI) may determine the final outcome in aneurismal subarachnoid hemorrhage (SAH) patients. This study is of interest to examine the efficacy of nano-particle curcumin (nanocurcumin), a diarylheptanoid, on a SAH-induced EBI model.

Methods: A rodent double hemorrhage model was employed. Nanocurcumin (75/150/300 μg/kg/day) was administered via osmotic mini-pump post-SAH. CSF samples were collected to examine IL-1β, IL-6, IL-8 and TNF-α (rt-PCR). Cerebral cortex was harvested for NF-κB (p50/p65) (western blot), caspases (rt-PCR) measurement.

Results: Nanocurcumin significantly reduced the bio-expression of NF-κB (p65), when compared with the SAH groups. The levels of IL-1β and IL-6 were increased in animals subjected to SAH, compared with the healthy controls, but absent in the high dose nanocurcumin+SAH group. Moreover, the levels of TNF-α in the SAH groups were significantly elevated. Treatment with nanocurcumin (300 μg/kg) reduced the level to the healthy control. The cleaved caspase-3 and -9a was significantly reduced in 300 μg/kg nanocurcumin treatment groups ($P<0.05$).

Conclusion: Treatment with nanocurcumin exerts its neuroprotective effect through the upward regulation of NF-κB (p65) and also reduced mitochondrion related caspase-9a expression.

Abbreviations: BA, basilar artery; caspases, cysteine requiring aspartate proteases; CSF, cerebrospinal fluid; EBI, early brain injury; ET, endothelin; HRP, horseradish peroxidase; IEL, internal elastic lamina; IL-1 and -6, interleukin 1 and 6; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, N-methyl-d-aspartate; Nrf2, nuclear factor-erythroid related factor 2; PBS, phosphate-buffered saline; PLGA, poly(lactic-co-glycolic acid); SAH, subarachnoid hemorrhage; TNF-α, tumor necrotic factor-α

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Besides, nanocurcumin decreased CSF levels of TNF-α and IL-1β, which may contribute to the extrinsic antiapoptotic effect. This study shows promise to support curcuminin, in a nanoparticle, could attenuate SAH induced EBI.

1. Introduction

Subarachnoid hemorrhage (SAH) remained a major cause of high morbidity and mortality in patients with a ruptured aneurysm (Dumont et al., 2003; Grosso, 2004; Kolias et al., 2009). Increased evidences revealed there were multifaceted mechanisms contributing to the final pathogenesis and still lead to poor manifestations. For years, despite efforts to reverse vasoconstriction of cerebral arteries, therapies trying to achieve better outcomes were not observed in SAH patients (Hansen-Schwartz et al., 2008; Kubo et al., 2008; Nishizawa et al., 2005; Provencio and Vora, 2005). Recently, SAH induced early brain injury (EBI), included cortical spreading depression, early cortical depolarization waves, and impairment of neurovascular coupling, is believed to play a significant role in deteriorated brain function among SAH patients (Ostrowski et al., 2006) .These acuminated results concerning the pathogenesis of SAH induced EBI encompass delayed neuron apoptosis contribute significantly to the high death and disability in both in vivo and in vitro studies (Garland and Rudin, 1998; Vikman et al., 2006). These findings stimulated efforts to dissect the cellular and molecular basis of EBI accompanying SAH to establish rational therapeutic targets.

Both molecular and cellular researches implicate oxyhemolysate in the subarachnoid space is sufficient to induce acute arteries and arteriolar constriction, passive venous obliteration and delayed arterial spasm (Aihara et al., 2001; Blake and Ridker, 2002; Clatterbuck et al., 2003; Grosso, 2004). The precise mechanism of this pathology remained unclear. An ongoing body of direct and indirect evidence publicized the mechanisms to produce EBI include oxidative stress (Dreier et al., 2009; Samuhasaneeto et al., 2009), nitric oxide(NO)/nitric oxide synthase(NOS) uncoupling (Shih et al., 2006), matrix metalloproteinase 9 (MMP-9) induced blood–brain barrier disruption (Ramos-Fernandez et al., 2011), modulation of nuclear factor erythroid related factor 2 (Nrf2) pathway, (Sasaki et al.,

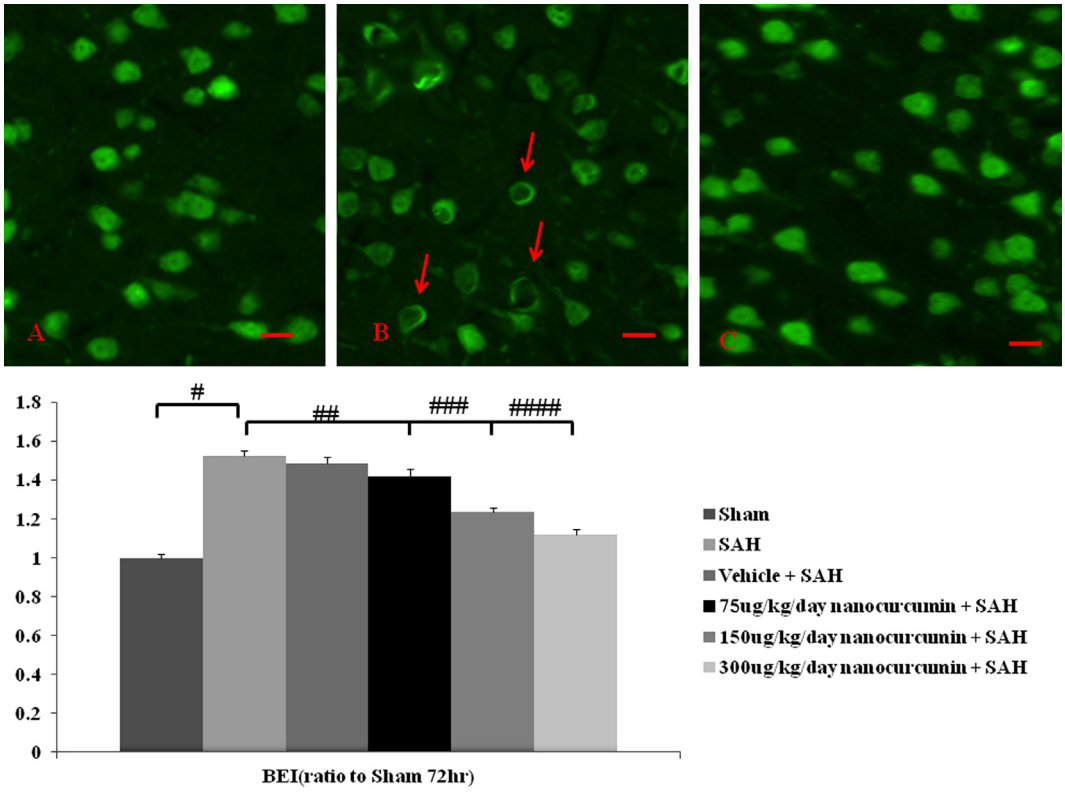

Fig. 1 – Bar graphs demonstrating brain edema index (BEI) after the induction of SAH. Upper panel: neuron from the harvested cortex was examined via NeuN immunostaining. (A) The sham operated group, (B) SAH groups and 300 μg/kg/day nanocurcumin treatment SAH groups (C). The vacuolated nuclei (arrow head) indicated the neuron apoptosis after SAH. Bottom panel revealed the brain edema index. #, ##, ###, ####: $P > 0.05$. Compared with the sham operated group. Standard bar = 200 μm.