Journal of Pharmacological Sciences xxx (2018) 1–8

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

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

Full paper

Resveratrol-loaded nanoemulsion prevents cognitive decline after abdominal surgery in aged rats

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ARTICLE INFO

Article history:
Received 28 May 2018
Received in revised form
12 August 2018
Accepted 17 August 2018
Available online xxx

Keywords:
Resveratrol
Neuroinflammation
Postoperative cognitive dysfunction
Microglia

ABSTRACT

The maladaptive response of aged microglia to surgery and consequent neuroinflammation plays a key pathogenic role in postoperative cognitive dysfunction (POCD). Here, we assessed the preventive effect of resveratrol (RESV) for POCD in aged rats. The emulsified form of RESV (*e*-RESV) was selected to improve its oral and brain bioavailability. Animals were assigned to one of four groups: *e*-RESV (80 mg/kg) versus vehicle treatment by abdominal surgery versus isoflurane anesthesia alone (n = 8 in each group). The dose-dependent effects of *e*-RESV were also assessed in dose range of 0–60 mg/kg. Either vehicle or *e*-RESV was administered intragastrically 24 h before surgery. Seven days after procedure, cognitive function was evaluated using a novel object recognition test, followed by measurement of hippocampal pro-inflammatory cytokine levels. Our results showed that pre-treatment with *e*-RESV attenuated the surgery-induced cognitive impairment and related hippocampal neuroinflammation at 40 mg/kg or higher doses. Additionally, the *ex-vivo* experiments revealed that the preemptive *e*-RESV regimen reduced the hippocampal microglial immune reactivity to lipopolysaccharide. Furthermore, *e*-RESV induced neuroprotective benefits were inhibited by the concomitant administration of sirtinol, a specific SIRT1 inhibitor. Our findings imply the preventive potential of *e*-RESV for POCD *via* the SIRT1 signaling pathway.

1. Introduction

There is an emerging concern that surgery may trigger and accelerate the age-related cognitive impairment, which is referred as postoperative cognitive dysfunction (POCD).[1] The development of POCD has been reported to be associated with long-term disability and increased mortality.[2] Although some preventive strategies for POCD have been proposed in preclinical studies, as well as small exploratory clinical trials, no established interventions are currently available.[3,4] Specifically, neuroinflammation, *i.e.*, a maladaptive microglial activation and overproduction of cytokines, is a key in the pathogenesis of neurodegenerative processes including Alzheimer's disease (AD) and POCD.[1,5–8] Our recent study reported that the postoperative neuroinflammation may transit from acute to chronic in an age- and hippocampal-specific manner, resulting in the development of POCD.[9] Therefore, the acute neuroinflammation during the early postoperative period may be critical therapeutic target for POCD.

Resveratrol (RESV), a polyphenol present in red wine, is well-known to have beneficial biochemical properties, including anti-aging and anti-neuroinflammatory effects.[10–12] Indeed, a preclinical study reported the protective effects of 12 weeks oral RESV treatment on aging-induced cognitive impairment.[12] In addition, a clinical trial for AD showed that chronic oral treatment with RESV for 53 weeks reduces pro-neuroinflammatory factors in cerebrospinal fluid, improving cognitive function.[13,14] Differing from the long-term progression of normal aging and AD, POCD is a consequence of the acute neuroinflammatory response triggered by the surgical procedure.[9] Therefore, acute, high-dose regimen during perioperative period may be appropriate for POCD prevention. However, our preliminary

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Peer review under responsibility of Japanese Pharmacological Society.

https://doi.org/10.1016/j.jphs.2018.08.006

study indicated that a preemptive injection with a single high-dose of free RESV, even at maximum administrable dose, failed to induce any neuro-cognitive protection in aged rats (Supplementary data 1). One plausible explanation for this may be due to the low bioavailability of RESV, particularly in the brain.[15] Alternatively, nanoemulsion based drug delivery systems has recently emerged as a promising strategy for overcome this issue, enhancing RESV solubility and improving permeation across the blood brain barrier.[16–20] Consistently, we hypothesized that nanoemulfised form of RESV can be effective for preventing the development of POCD.

RESV-induced neuroprotection is thought to be mainly mediated by allosteric activation of sirtuin-1 (silent mating type information regulation 2 homolog 1; SIRT1), a major gene associated with longevity.[10,21] SIRT1 is an evolutionarily conserved mammalian nicotinamide adenine dinucleotide-dependent protein deacetylase that is implicated in a wide range of aging-related diseases.[22] As SIRT1 is also reported to regulate microglial activity,[23] we further hypothesized that preoperative RESV treatment can act as an anti-neuroinflammatory agent *via* the SIRT1 pathway.

To test our hypothesis, we investigated the effects of a preoperative single dose of RESV-loaded nanoemulsion (emulsified RESV; *e*-RESV) on the development of POCD in an aged rat model of abdominal surgery. The effects of *e*-RESV on the microglial phenotype in the hippocampus were also assessed in *ex-vivo* preparations.

2. Materials and methods

2.1. Animals and experimental designs

All experiments were approved by the Institutional Animal Care and Use Committee of Kochi Medical School. Wistar male rats aged 19–22 months were purchased from Alfresa Shinohara Chemicals Corporation (Kochi, Japan). The animals were divided into three sets of experiments (Fig. 1). Experiment-1 assessed the effects of *e*-RESV on POCD using a 2 × 2 experimental design: *e*-RESV (maximum dose; 80 mg/kg) versus vehicle emulsion of *e*-RESV (*e*-vehicle) treatment by abdominal surgery versus anesthesia alone (n = 8 in each group). Experiment-2 was conducted to observe the dose-dependent effects of *e*-RESV (0, 2.0, 20, 40, or 60 mg/kg; n = 6 in each dose group). In Experiment-3, to perform the SIRT1-related antagonist experiment using a specific SIRT1 inhibitor, sirtinol, surgical animals were randomly assigned to four treatment groups (n = 8 in each group): dimethyl sulfoxide (DMSO, a vehicle of sirtinol) with *e*-vehicle treated, sirtinol (5.0 mg/kg) with *e*-vehicle

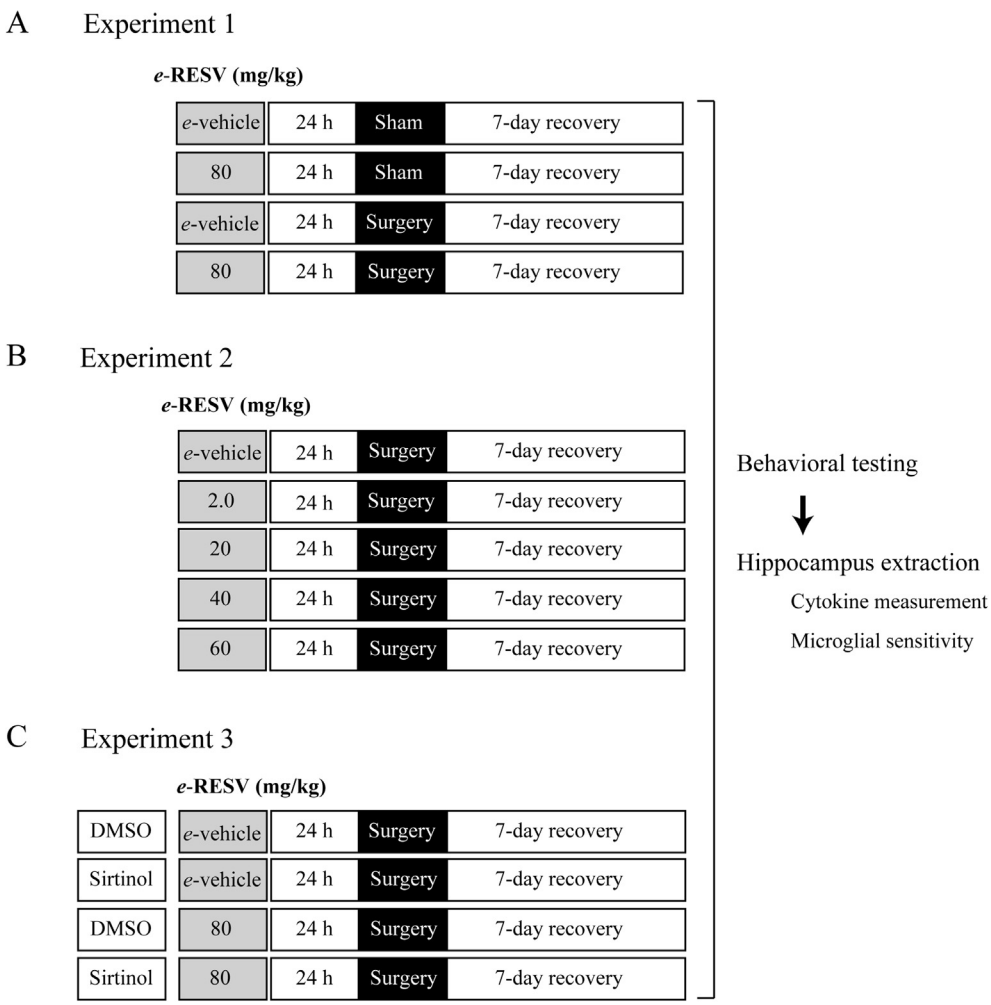

Fig. 1. Schematic diagram of the three different experimental protocols. (**A**) Experiment-1; Effects of emulsified resveratrol (*e*-RESV, 80 mg/kg) on postoperative cognitive impairment and related neuroinflammation (n = 8 in each group). (**B**) Experiment-2; Dose-dependent effects of *e*-RESV (0–60 mg/kg, n = 6 in each group). (**C**) Experiment-3; Antagonist study using sirtinol (n = 8 in each group).

Please cite this article in press as: Locatelli FM, et al., Resveratrol-loaded nanoemulsion prevents cognitive decline after abdominal surgery in aged rats, Journal of Pharmacological Sciences (2018), https://doi.org/10.1016/j.jphs.2018.08.006