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BRAIN RESEARCH

Research Report

Inhibition of excitatory synaptic transmission by *trans*-resveratrol in rat hippocampus

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ABSTRACT

The red wine polyphenol *trans*-resveratrol has been found to exert potent protective actions in a variety of cerebral ischemia models. The neuroprotection by *trans*-resveratrol thus far is mainly attributed to its intrinsic antioxidant properties. In the present study, the effects of the red wine polyphenol on excitatory synaptic transmission were investigated in the CA1 region of rat hippocampal slices. Perfusion with *trans*-resveratrol (10–100 μM) caused a concentration-dependent inhibition on the filed excitatory postsynaptic potentials (the field EPSPs) without detectable effect on the presynaptic volleys. The inhibition had a slow onset and was reversible. *Trans*-resveratrol (30 μM) did not change the ratios of paired-pulse facilitation of the field EPSPs tested at intervals of 20, 40 and 80 ms, nor did it alter the membrane properties of postsynaptic CA1 pyramidal neurons. However, *trans*-resveratrol (30 μM) significantly suppressed glutamate-induced currents in postsynaptic CA1 pyramidal neurons. In dissociated hippocampal neurons, the IC_{50} value of *trans*-resveratrol in inhibition of glutamate-induced currents was 53.3±9.4 μM. Kainite and NMDA receptors were more sensitive to the red wine polyphenol than AMPA receptors. The present study for the first time demonstrates that *trans*-resveratrol inhibits the postsynaptic glutamate receptors, which probably works in concert with its antioxidant action for ameliorating the brain ischemic injury. The findings also support the future use of *trans*-resveratrol in the treatment of various neurodegenerative disorders.

1. Introduction

The red wine polyphenol *trans*-resveratrol (*trans*-3,4′,5-trihydroxystilbene) has been demonstrated to possess a variety of biological activities, such as cardiovascular protection, anti-inflammatory and anti-cancer effects and so on (Frémont, 2000). In the recent years, the red wine polyphenol was found to exert potent protective actions in several animal models of cerebral ischemia and seizures. For instance, *trans*-resveratrol was demonstrated to be effective against the cerebral ischemic injury (Huang et al., 2001; Inoue et al., 2003; Sinha et al., 2002; Wang et al., 2002) and kainate-induced seizures and neurotoxicity (Gupta et al., 2002; Virgili and Contestabile, 2000; Wang et al., 2004) in rodents. Furthermore, it was also found to ameliorate the cell damage and death in cultured neuronal preparations caused by a β-amyloid peptide (Aβ) fragment, nitric oxide (NO), oxidized lipoproteins and so on (Bastianetto et al., 2000; Draczynska-Lusiak et al., 1998; Han et

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al., 2004; Nicolini et al., 2001; Savaskan et al., 2003; Sun et al., 2002). However, the mechanisms underlying the neuroprotective effects remain to be elucidated.

Excitotoxicity and oxidative stress are two main causes responsible for the neuronal damage during the hypoxia/ischemic insult to brain (Coyle and Puttfarcken, 1993; Lipton and Rosenberg, 1994; Sun and Chen, 1998). Numerous recent studies showed that the antioxidant action (scavenging lipid hydroperoxyl-free radicals and hydroxyl and superoxide anion radicals) of *trans*-resveratrol contributes to its neuroprotective actions (Bastianetto et al., 2000; Gupta et al., 2002; Savaskan et al., 2003; Sinha et al., 2002). On the other hand, the beneficial effects of glutamate receptor antagonists (NMDA receptor antagonists, in particularly) were demonstrated in various models of cerebral ischemia *in vivo* and *in vitro* (Lipton and Rosenberg, 1994). Thus far, however, there is no evidence showing that the red wine polyphenol may antagonize the glutamate-induced excitotoxicity. In the present study, the actions of *trans*-resveratrol on the glutamatergic neurotransmission were investigated in the CA1 region of rat hippocampus.

2. Results

2.1. *Effects of trans-resveratrol on excitatory synaptic transmission in hippocampal slices*

In the CA1 region, extracellular field potentials were elicited by stimulating the Schaffer collateral–commissural fibers and recorded in the stratum radiatum. Perfusion of *trans*-resveratrol (30 μM) caused a slowly developed reduction in the amplitudes of the field excitatory postsynaptic potentials (the field EPSPs) without significant change in the presynaptic volleys (Fig. 1A). The time course of the inhibition of the field EPSPs by *trans*-resveratrol (30 μM) was shown in Fig. 1B. The inhibition started at 5 min and reached a steady-state level about 40 min after the start of perfusion. The field EPSPs were fully recovered upon washout for 20 min. Moreover, the inhibition of the field EPSPs by *trans*-resveratrol was concentration dependent (Fig. 1C). The threshold concentration was around 3 μM; and *trans*-resveratrol at 10, 30 and 100 μM inhibited the field EPSPs by 25 ± 4%, 64 ± 10% and 70 ± 8%, respectively.

2.2. *Trans-resveratrol did not act at a presynaptic locus*

The lack of effect of *trans*-resveratrol on the presynaptic volleys was further demonstrated when the input/output relationship of the extracellular field potentials was investigated. In a representative experiment shown in Fig. 2A, *trans*-resveratrol (30 μM) did not change the threshold of the presynaptic volleys and their sizes over the entire range of the stimulation durations. However, the threshold of the field EPSPs was changed from 20 μs to 60 μs after perfusion with *trans*-resveratrol (30 μM) for 40 min (Fig. 2B). Meanwhile, the amplitudes of field EPSPs elicited with the stimulation durations of 60, 70, 80 and 90 μs were drastically reduced (0.52, 0.59, 0.64 and 0.64 mV, respectively, before perfusion with *trans*-resveratrol; 0.10, 0.14, 0.23 and 0.34 mV, respectively, in the presence of *trans*-resveratrol). Similar results were observed in all 6 slices tested. The results demonstrated that the red wine polyphenol did not affect the presynaptic volley activities.

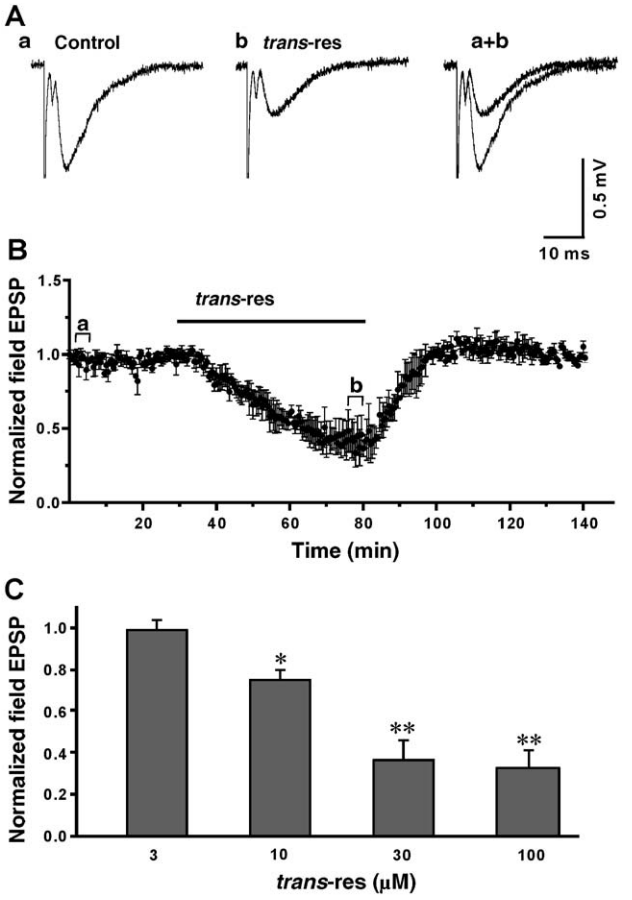

Fig. 1 – Inhibition of the excitatory synaptic transmission by *trans*-resveratrol in hippocampal slices. (A) Extracellular field potentials recorded in the CA1 region before and after perfusion with *trans*-resveratrol (30 μM) for 40 min in a representative experiment. Each trace is the average of ten consecutive records. On the right, the two traces are superimposed. (B) Plot of the field excitatory postsynaptic potentials (the field EPSPs) against time. The potentials were elicited every 30 s. Each symbol is the mean ± SEM from 5 slices. Black bar denotes the perfusion with *trans*-resveratrol (30 μM). The brackets (a and b) indicate two periods of time, in which the representative traces in panel A were taken. (C) Bar graphs showing the concentration-dependent inhibition of the field EPSPs by *trans*-resveratrol (n=5 for each concentration, $^{*}P<0.05$, $^{**}P<0.01$ vs. control).

A homosynaptic paired-pulse facilitation (PPF) paradigm was used to further address the site of action of *trans*-resveratrol. PPF is a short lasting presynaptic alteration in synaptic efficacy, determined by the probability of neurotransmitter release. A high PPF ratio indicates a high release probability from presynaptic nerve terminals (Debanne et al., 1996). If the inhibition of the field EPSPs by *trans*-resveratrol had involved a presynaptic mechanism, it would have been associated with alternation in PPF ratios. Before perfusion with *trans*-resveratrol, PPF ratios tested at the interval of 20, 40 and 80 ms in 5 slices were 1.58 ± 0.09, 1.61 ± 0.09 and 1.47 ± 0.06,