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Research report

Trans-astaxanthin attenuates lipopolysaccharide-induced neuroinflammation and depressive-like behavior in mice

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ABSTRACT

Mounting evidence supports that inflammation and increased cytokine levels are associated with depression-like symptoms and neuropsychological disturbances in humans. Trans-astaxanthin has anti-inflammatory and antioxidative activity, also has the ability to cross the blood-brain barrier in rodents. Here, we investigated the effects of trans-astaxanthin on lipopolysaccharide (LPS)-induced depressive-like behavior in mice. In both the forced swimming test (FST) and tail suspension test (TST), the immobility time was increased when mice were administrated with a single dose of LPS (0.83 mg/kg, i.p.). However, this alteration can be reversed by pretreatment of trans-astaxanthin at doses of 20, 40 and 80 mg/kg (p.o.) for 7 days. Further neurochemical assays suggested that LPS-induced overexpression of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) in the hippocampus and the prefrontal cortex (PFC) can also be reversed by trans-astaxanthin treatment. Moreover, trans-astaxanthin at 80 mg/kg was demonstrated to effectively antagonize iNOS, nNOS and COX-2 expression, both at mRNA and protein levels, nitric oxide (NO) levels, via regulating NF-κB in the hippocampus and PFC. Taken together, trans-astaxanthin may serve as an effective therapeutic agent for LPS-induced depressive-like behavior via its potent anti-inflammatory property.

1. Introduction

Mounting evidence suggests a close linkage between neuroinflammation and depression (Miller and Raison, 2015; Krogh et al., 2014). Recently, some studies have demonstrated that neuroinflammation in some depression models is characterized by the release of proinflammatory cytokines and activation of nuclear factor-kappaB (NF-κB) (Monje et al., 2011; Koo et al., 2010). The study by Chen et al. (Chen et al., 2016) has shown that mice subjected to acute stress restraint exhibit depression-like behavior, with increased nitric oxide synthase (NOS) level in the hippocampus. Additionally, patients who suffer from depression exhibit high levels of pro-inflammatory cytokines and other inflammatory mediators in the prefrontal cortex (PFC) and hippocampus (Janssen et al., 2010; Hannestad et al., 2011). Taken together, these observations provide evidence that prevention of inflammatory disturbances, especially in the hippocampus and PFC, could be a therapeutic avenue for depression.

The acute administration of cytokine inducer lipopolysaccharide (LPS) is a widely-accepted animal model to investigate the relationship between neuroinflammation and depressive symptoms (Hart, 1988; Mello et al., 2013; Lawson et al., 2013). The depressive-like behaviors induced by administration of LPS, such as hypoactivity in the force swimming test and the tail suspension test, can be reversed by antidepressant treatments (Yirmiya, 1996; Ohgi et al., 2013). These studies also revealed that LPS-treated mice exhibited oxidative damage and increased abnormal genes and proteins expression. Indeed, behavioral deficits can be observed in LPS-stimulated animal model together with elevated NOS expression, increased pro-inflammatory cytokine levels and NF-κB activation in the hippocampus and some other brain regions (Tomaz et al., 2014; Ndongson et al., 2015; Wang et al., 2014).

Trans-astaxanthin (ASX), a red carotenoid pigment, is rich in algae, plants and a limited number of fungi and bacteria. It is endowed with a variety of pharmacological effects, including anti-inflammatory and antioxidative activity (Wu et al., 2015; Balietti et al., 2016; Riccioni et al., 2012). It also has the ability to locate either inside the phospholipid membrane or on the membrane surface (Goto et al., 2001) and to cross the blood-brain barrier in rodents (Tso and Lam, 1996). As neuroinflammatory plays a critical factor in the pathophysiology of depression, we reasoned that trans-astaxanthin may also have therapeutic potentials in fighting depression.

In the present study, we investigated the possible role of

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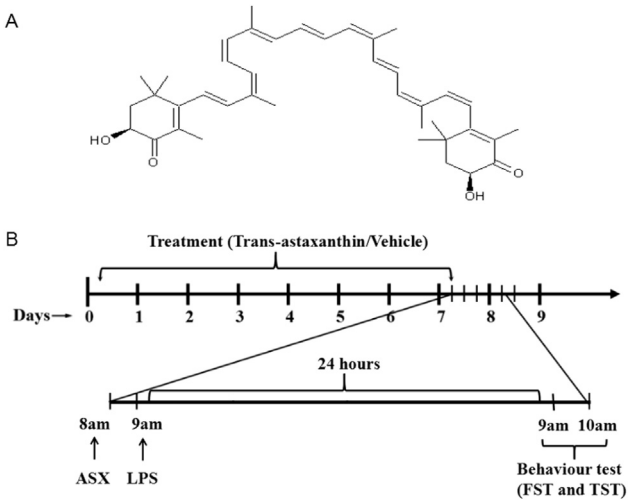

Fig. 1. (A) Structure of trans-astaxanthin (ASX). (B) Experimental protocol schedule. Mice received administration of ASX (20, 40, 80 mg/kg, p.o.) or vehicle (CMC-Na, p.o.) for 7 days. LPS or vehicle were injected on day 7 after ASX treatment, then behavior test were done at 6 h, 12 h and 24 h after LPS injection. Animals were sacrificed immediately after behavior test for neurochemical analysis.

neuroinflammation in the anti-depressant-like effect of trans-astaxanthin through various behavioral paradigms. In addition, the expression levels of brain pro-inflammatory cytokines, NOS, NO, TNFα and COX-2, as well as NF-κB were tested by neurochemical and biochemical assays to confirm whether the anti-depressive actions of trans-astaxanthin are related to alteration of neuroinflammation (Fig. 1).

2. Result

2.1. Effects of treatment with trans-astaxanthin on the FST and TST

Effects of trans-astaxanthin on the immobility time [$F(5, 54) = 8.66$, $p < 0.001$] in FST are shown in Fig. 2A. LPS stimulation caused a significant increase in the duration of immobility when compared with saline-treated mice ($p < 0.001$). However, treatment with trans-astaxanthin (40 and 80 mg/kg) abolished the adverse effect of LPS ($p < 0.05$ and $p < 0.01$), and trans-astaxanthin exerted this effect in a dose-dependent manner.

Similar findings were obtained in the TST [$F(5, 54) = 9.25$, $p < 0.001$]. LPS induced a significant increase in immobility time in TST ($p < 0.001$) (Fig. 2B), and treatment with trans-astaxanthin (40 and 80 mg/kg) abolished this adverse effect of LPS ($p < 0.01$ and $p < 0.001$).

2.2. Effects of pre-treatment with trans-astaxanthin on the locomotor activity

In order to eliminate the excitatory or inhibitory effects of LPS and trans-astaxanthin on behavior test, we tested the locomotion counts before FST and TST. As shown in Fig. 3, no significant difference was found among the five groups in all parameters evaluated in the locomotor activity. These results indicated that LPS or trans-astaxanthin does not affect spontaneous locomotor activity.

2.3. Effect of pre-treatment with trans-astaxanthin on LPS-induced NF-κB activation in the hippocampus and PFC

As presented in Fig. 4, LPS administration led to significant changes in the phosphorylation of NF-κB p65 in the hippocampus [$F(5, 30) = 12.55$, $p < 0.001$] and PFC [$F(5, 30) = 11.59$, $p < 0.001$].

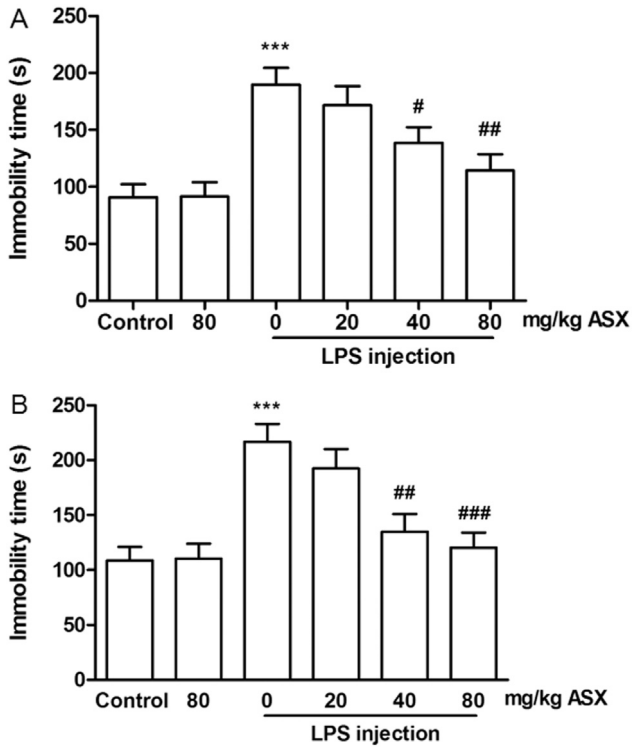

Fig. 2. Effect of ASX on the immobility time in the force swimming task (A) and tail suspension task (B) in mice. Mice were administered vehicle, ASX (20, 40 and 80 mg/kg) for 7 days before LPS treatment. The immobility time of force swimming task and tail suspension task were assessed 24 h after injection of saline or LPS. Values were the mean ± S.E.M. with 10 mice in each group. $^{***}P < 0.001$ vs. the vehicle-treated control group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ vs. the vehicle-treated LPS group.

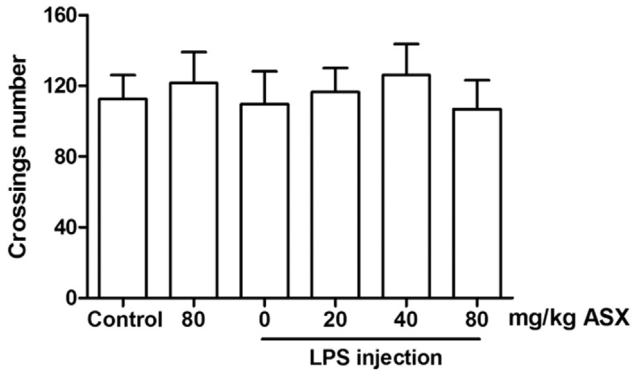

Fig. 3. Effect of ASX on locomotor activity in mice. Mice were administered vehicle, ASX (20, 40 and 80 mg/kg) or LPS before testing. The locomotion counts were recorded for 10 min. Values were the mean ± S.E.M. with 10 mice in each group.

The phosphorylation of NF-κB p65 significantly increased in the hippocampus and PFC after LPS treatment when compared with control group ($p < 0.001$ and $p < 0.001$). Pretreatment with 80 mg/kg trans-astaxanthin suppressed LPS-increased NF-κB p65 phosphorylation level in the hippocampus and PFC ($p < 0.01$ and $p < 0.01$). Moreover, no change of NF-κB p65 phosphorylation level was observed after trans-astaxanthin pretreatment in normal mice.

2.4. Effects of trans-astaxanthin on NO levels in the hippocampus and PFC

The level of NO detected in the hippocampus and PFC are summarized in Fig. 5. One-way ANOVA showed significant