JOURNAL OF FUNCTIONAL FOODS 5 (2013) 601–606

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Medium-chain fatty acid-containing dietary oil alleviates the depression-like behaviour in mice exposed to stress due to chronic forced swimming

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ARTICLE INFO

Article history:
Received 11 September 2012
Received in revised form
18 December 2012
Accepted 31 December 2012
Available online 31 January 2013

Keywords:
Medium-chain fatty acid
Dietary oil
Depression
Forced swimming test
Extracellular signal-regulated kinases 1/2

ABSTRACT

Antidepressant-like effects of medium-chain fatty acid-containing dietary oil were examined by using mice forced to swim. This stress loading induced features typical for depression such as depressive symptoms and decreased the ratio of phosphorylated (p) extracellular signal-regulated kinases (ERK)1/2 to ERK1/2 in the hippocampus, demonstrating that our animal model prepared in mice was comparable to the general models using rats. Test diets containing structured medium- and long-chain triacylglycerols (MLCTs) and/or long-chain triacylglycerols (LCTs) as test oils and tap water were given freely during the stress period. Consequently, the intake of MLCTs resulted in a significant reduction in the immobility time in the forced swim test. Moreover, the ratio of pERK1/2 to ERK1/2 in the hippocampus was significantly higher in mice fed the MLCT diet than in those fed the LCT one. These results are the first evidence showing that MLCTs have a preventive effect against forced swimming-induced depression-like symptoms.

1. Introduction

Depression is a kind of mood disorder, and an illness with lasting emotional and physical manifestations (Nestler et al., 2002). Depression adversely affects a patient's quality of life by causing deterioration in diet and physical activity; and the costs for treatment of depression are very huge in developed countries (Greenberg et al., 2003), demonstrating that depression is a serious problem for not only patients but also health care cost. Since patients with depression are now increasing in number in Japan due to stressful social circumstances such as the ongoing economic recession, certain countermeasures against depression are urgently needed. Such patients could greatly reduce their symptoms if they could protect themselves against depression through their daily diet.

Mechanisms underlying the onset of depression and the intracellular factors subsequently regulating depression-like behaviour are still largely unknown. Extracellular signal-regulated kinases 1/2 (ERK1/2), members of the mitogen-activated kinase (MAPK) family, are key molecules in many signal transduction pathways such as the Ras/MAPK pathway, which is triggered by receptor tyrosine kinases. The activity of ERK1/2 has recently been considered to be involved in the mechanisms giving rise to depression symptoms (Duman, Schlesinger, Kodama, Russell, & Duman, 2007; Gourley et al., 2008; Qi et al., 2009). We recently found that medium-chain fatty acids (MCFAs) and their methyl or ethyl esters facilitate the phosphorylation of ERK1/2 in neurons cultured from embryonic rat brain, and showed that 2-decenoic acid ethyl ester: {(E)-ethyl dec-2-enoate} (DAEE) has the most potent activity of the compounds tested (Makino et al., 2010).

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1756-4646/$ - see front matter
http://dx.doi.org/10.1016/j.jff.2012.12.006

Furthermore, we found out that intraperitoneally administered DAEE acts like an antidepressant drug, significantly preventing or being therapeutic against depression. Namely, DAEE protected against the depression and anxiety symptoms when administered intraperitoneally to the mice once a day for 3 weeks simultaneously with the mild chronic stress loading, or improved quickly these symptoms when administered after stress loading (Makino et al., unpublished results). MCFAs, composed of chains of 8 to 10 carbon atoms, are found in edible oils such as coconut oil. Compared with long-chain fatty acids (LCFAs), MCFAs have several unique physiological and biological characteristics, and are utilized to prevent obesity and several lifestyle-related diseases (Bach & Babayan, 1982). Previously, we developed medium- and long-chain fatty acid-containing dietary oils (MLCTs), which are lipids randomly structured with LCFAs and MCFAs in the same glycerol molecule (Negishi, Shirasawa, Arai, Suzuki, & Mukataka, 2003). When long-chain triacylglycerols (LCTs) in the daily diet are replaced by MLCTs in human and rat studies, the accumulation of body fat is significantly lower (Kasai et al., 2003; Matsuo & Takeuchi, 2004; Shinohara, Ogawa, Kasai, & Aoyama, 2005).

To evaluate antidepressant-like effects of these functional oils, MLCTs, we compared the effects of MLCTs with those of LCTs on mice with depression induced by chronic forced swimming. Our results showed that MLCTs significantly alleviated the depression symptoms and increased the levels of phosphorylated ERK1/2 in the hippocampus, when compared with LCTs.

2. Materials and methods

2.1. Materials

Canola oil as LCTs, and MLCTs as randomly inter-esterified triacylglycerols containing MCFAs and LCFAs in the same glycerol molecule, were obtained from Nisshin OilliO, Ltd. (Tokyo, Japan) and used as the control and test oils, respectively. Canola oil contained 5.2% palmitic acid, 2.1% stearic acid, 61.8% oleic acid, 19.6% linoleic acid, 7.3% linolenic acid, and 4.0% other fatty acids. MLCTs contained 8.7% octanoic acid, 2.8% decanoic acid, 3.7% palmitic acid, 1.7% stearic acid, 52.7% oleic acid, 18.2% linoleic acid, 9.5% linolenic acid, and 2.7% other fatty acids. Fatty acid composition is expressed as a weight percentage of the total amount of fatty acids measured.

2.2. Animals and diets

Six-week-old male ddY mice were purchased from Japan SLC (Hamamatsu, Japan). The ddY strain is an outbred one, and has been maintained as a closed colony. Mice of the strain show good reproductive performance and superior growth. In Japan, this strain has been widely used for various fields of researches. The mice were divided into 2 groups ($n = 5–6$) and housed under conditions of controlled temperature (21–23 °C), humidity (55–65%), and lighting (lights on from 08:00 to 20:00) and fed a commercial standard diet (Labo MR stock, Nihon Nosan, Tokyo, Japan) with tap water freely available. All animal experiments were carried out according to the Guideline for Care and Use of Laboratory Animals of Gifu Pharmaceutical University. To evaluate the effect of the test oils, we formulated the experimental diets according to the AIN-93G diet (Reeves, Nielsen, & Fahey, 1993), which was modified to contain sucrose at 40 g/kg of diet and pregelatinized instead of dextrinized cornstarch, and contained 7% LCTs or MLCTs as test oils. The diets were manufactured as chow and were given freely together with tap water.

2.3. Stress-loading procedure and forced swimming test (FST)

The model mice with depression-like symptoms were prepared by exposure to stress caused by chronic forced swimming. The procedure used was a modification of that originally reported by Qi, Lin, Li, Pan, and Wang (2006) and Qi et al. (2008), who used rats. Briefly, mice were placed individually into 5 L polypropylene beakers (height 27 cm, diameter 27 cm) filled with 4 L of water (25 ± 1 °C) and kept there for 6 min. Each mouse was forced to swim individually for 6 min once a day for 14 consecutive days. A mouse was judged to be immobile when it floated in an upright position, and made only small movements to keep its head above water. The duration of immobility was recorded during the last 4 min of the 6 min testing period.

2.4. Elevated plus maze test (EPMT)

After the mice had been stressed as described above, they were subjected to a modified version of EPMT described previously (Walf & Frye, 2007). The experimental apparatus for this test was shaped like a "plus" sign and consisted of a central platform (6 × 6 cm), 2 open arms (30 × 6 cm), and 2 equal-sized closed arms (30 × 6 × 10 cm) opposite to each other. The maze was made of wood and elevated to a height of 62 cm above the floor. The test consisted of placing a mouse in the central platform facing an open arm and allowing it to freely explore the maze for 5 min. Anxiolytic activity was indicated by an increase in the time spent in the open arms; and anxiety, by a decrease in this measurement. Additionally, the number of entries into both the closed and open arms was recorded as an indicator of locomotor activity of the animals in this test.

2.5. Tissue dissection and processing

Mice were sacrificed 48 h after the end of the chronic forced swim stress, and their brains were rapidly removed and placed on ice. The entire hippocampus was dissected from the brain, and homogenized in lysis buffer {20 mM Tris–HCl buffer (pH 7.4) containing 150 mM NaCl, 2 mM EDTA, 1% NP-40, 50 mM NaF, 0.1% sodium dodecyl sulphate (SDS), 1% Na deoxycholate, 1 mM Na_3VO_4, 1 mM phenylmethylsulphonyl fluoride and 10 μg/ml aprotinin and leupeptin} used at 20 times the volume of the tissue. The protein content of lysates was determined by using a BCA protein assay kit (Pieace Biotechnology Inc., Rockford, IL, USA). Lysates were mixed with SDS solution for electrophoresis. All the sample solutions were stored at −20 °C until used.