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Influence of lifelong dietary fats on the brain fatty acids and amphetamine-induced behavioral responses in adult rat

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ABSTRACT

The influence of dietary fatty acids (FA) on mania-like behavior and brain oxidative damage were evaluated in rats. First generation of rats born and maintained under supplementation with soybean-oil (SO), fish-oil (FO) or hydrogenated-vegetable-fat (HVF), which are rich in n−6, n−3 and *trans* (TFA) FA, respectively, until adulthood, were exposed to an amphetamine (AMPH)-induced mania animal model to behavioral and biochemical evaluations.

While AMPH caused hyperlocomotion in HVF and, to a less extent, in SO- and FO-groups, a better memory performance was observed in FO group. Among vehicle-groups, HVF increased reactive species (RS) generation and protein-carbonyl (PC) levels in cortex; FO reduced RS generation in hippocampus and decreased PC levels in hippocampus and striatum. Among AMPH-treated animals, HVF exacerbated RS generation in all evaluated brain areas and increased PC levels in cortex and striatum; FO reduced RS generation in hippocampus and decreased PC levels in hippocampus and striatum. FO was related to higher percentage of polyunsaturated fatty acids (PUFA) and docosahexaenoic acid (DHA) in cortex and striatum, while HVF was associated to higher incorporation of TFA in cortex, hippocampus and striatum, besides increased n−6/n−3 FA ratio in striatum. While a continuous exposure to TFA may intensify oxidative events in brain, a prolonged FO consumption may prevent mania-like-behavior; enhance memory besides decreasing brain oxidative markers. A substantial inclusion of processed foods, instead of foods rich in omega-3, in the long term is able to influence the functionality of brain structures related to behavioral disturbances and weaker neuroprotection, whose impact should be considered by food safety authorities and psychiatry experts.

1. Introduction

Bipolar disorder (BD) is a chronic condition closely related to recurring episodes that affects about 2.4% of the world adult population (Merikangas et al., 2011), and it may be considered one of the most debilitating illnesses (Magalhaes et al., 2012). While BD remains poorly understood, its pathophysiology has been related to processes which include failures in the neuronal plasticity and neurotransmission (Coyle and Duman, 2003; Manji et al., 2001) and inflammatory and oxidative damages (Berk et al., 2011). Given that the clinical symptoms of BD include manic episodes with exaltation, irritability and hyperactivity, amphetamine (AMPH) administration is able to induce manic symptoms in normal human volunteers (Strakowski and Sax, 1998) and causes hyperlocomotion in animals, making this psychostimulant drug a predictor and well-established model of mania (Frey et al., 2006; Machado-Vieira et al., 2004). In fact, AMPH is able to exacerbate the monoaminergic neurotransmission, whose metabolic consequence resulting from autoxidation and deamination is increased reactive species (RS) production (Graham et al., 1984; McCann et al., 1998). Development of oxidative stress may be the primary outcome of RS excess, especially in dopaminergic brain areas, whose cascading events are related to oxidation of lipids and proteins, affecting also the mitochondrial function (Berman and Hastings, 1999). In this sense, the generation of RS was recognized to play a fundamental role in the pathogenesis of neuropsychiatric conditions (Halliwell, 2001; Palmieri and Sblendorio, 2006), including BD (Andreazza et al., 2007; Frey et al., 2007; Steckert et al., 2010).

Abbreviations: PUFA, polyunsaturated fatty acids; SO, soybean oil; FO, Fish oil; HVF, hydrogenated vegetable fat; TFA, *trans* fatty acids; AMPH, Amphetamine; RS, Reactive species; PC, Protein carbonyl; BP, Bipolar disorder; MUFA, monounsaturated fatty acids; FA, fatty acids; EFA, essential fatty acids; LC-PUFA, long chain polyunsaturated fatty acids; ALA, α-linolenic acid; LA, linoleic acid; DHA, docosahexaenoic acid; EPA, Eicosapentaenoic acid; ARA, Arachidonic acid; NORT, Novel recognition task.

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The composition of fatty acids (FA) is closely related to biophysical properties of the membranes, exerting influence on neurotransmission. Such considerations are based on the fact that the different dietary FA may affect the composition of neuronal membranes, especially during pregnancy and lactation (Mazza et al., 2007), affecting their fluidity, plasticity and function (Jump, 2002). Considering the growing consumption of processed foods in Western countries, recent reports have associated their chronic intake with development of neuropsychiatric diseases (De Leon et al., 2002; Richardson and Ross, 2000; Vancassel et al., 2001). In fact, processed foods are rich in *trans* fatty acids (TFA), and their consumption can represent a loss of essential fatty acids (EFA), especially those of the n−3 series (n−3 EFA). The incorporation of these FA into membrane phospholipids is fundamental to maintain membrane integrity, thus preserving the brain physiologic functions (Acar et al., 2003; Teixeira et al., 2011, 2012; Trevizol et al., 2011; Wandall, 2008). Of particular importance, while a higher incorporation of n−3 polyunsaturated fatty acids (PUFA) has been related to increased fluidity of the brain membranes and a balanced density and activity of receptors (Yehuda et al., 2005), the presence of TFA in these membranes has been associated with memory loss, anxiety-like symptoms (Teixeira et al., 2011), and movement disorders (Teixeira et al., 2012) in old age. PUFA can be classified in two main families: n−3 PUFA or omega-3 and n−6 PUFA or omega-6, which are found in some cold-water fish species and in oil seeds, respectively. These PUFA are represented by the linolenic acid (ALA; 18:3n−3) and linoleic acid (LA; 18:2n−6), which are metabolic precursors of the long-chain polyunsaturated fatty acids (LC-PUFA), such as eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3), as well as arachidonic acid (ARA; 20:4n−6), respectively (Benatti et al., 2004; Holub, 2002; Innis, 2003; Simopoulos, 1999). Besides being functional components of neural membrane phospholipids (Rapoport, 2001), DHA, EPA and ARA are also substrates for cyclooxygenase-2 (COX-2) (Bagga et al., 2003), whose activity on n−6 and n−3 PUFA generates prostaglandins of series 2 (PGE2) and 3 (PGE3), respectively (Bagga et al., 2003). Since consumption of different fats can affect the FA composition of brain membrane phospholipids (Mahfouz et al., 1984), PGE3 derivatives are less pro-inflammatory than n−6 derivatives, providing greater protection against oxidative damages (Bagga et al., 2003).

Whereas previous studies by our research group showed that high intakes of TFA after weaning and until adulthood may facilitate the development of mania-like behavior, some studies showed that a higher incorporation of dietary FA by brain membranes occurs primarily during the perinatal period (Neuringer et al., 1988), significantly affecting their composition, structure and function (Fernstrom, 1999). Based on this, the aim of this study was to evaluate the influence of isocaloric supplementation of soybean oil (SO), fish oil (FO) and hydrogenated vegetal fat (HVF) as sources of n−6, n−3 and TFA, respectively, on development of AMPH-induced mania-like behavior in first generation rats, which were conceived, born and grown (until adulthood) under the same supplementation as their dams.

2. Experimental procedures

2.1. Animals and experimental design

All procedures with animals were approved by the Ethical Research Committee of the Federal University of Santa Maria (UFSM-24/2010), which is affiliated to the Council for Control of Animal Experiments (CONCEA), following international norms of care and animal maintenance, and that all efforts were made to minimize the number of animals used and their suffering.

Animals were kept in Plexiglas cages with free access to food and water in a room with controlled temperature (23 °C ± 1 °C) and on a 12 h-light/dark cycle throughout the experimental period. One week before mating, female adult Wistar rats (n = 8) were supplemented (3 g/kg; p.o.) (Ferraz et al., 2011) with either soybean oil (SO), which was an isocaloric control group, fish oil (FO) or hydrogenated vegetable fat (HVF) and maintained under the same supplementation during pregnancy and lactation. From weaning (postnatal day 21), one male pup from each litter (n = 8) and the same supplementation was grouped (five per cage) and kept under the same oral treatment until 90 days of age. SO and HVF were purchased in a local supermarket and FO was donated by Herbarium® (Curitiba, Brazil).

At 90 days of age, one half of each experimental group was submitted to an animal model of mania, while the other half was treated with saline. Rats received a single daily injection of amphetamine (AMPH − 4 mg/kg/ip) for 14 days (adapted from Frey et al., 2006) and submitted to behavioral observations.

2.2. Fatty acid (FA) composition of supplementations

Oil and fat samples (SO, FO and HVF) were submitted to saponification in methanolic KOH solution and esterification in methanolic H_2SO_4 solution (Hartman and Lago, 1973). Methylated fatty acids were analyzed using an Agilent Technologies gas chromatograph (HP 6890) equipped with a Supelco SP-2560 capillary column (100 m × 0.25 mm × 0.20 μm) and flame ionization detector. The temperature of the injector port was set at 250 °C and the carrier gas was nitrogen (1.0 mL/min). After injection (1 μL, split ratio 50:1), the oven temperature was kept at 70 °C for 4 min, raised to 180 °C at 9 °C/min and held at this temperature for 2 min, raised to 200 °C at 7 °C/min and held at this temperature for 5 min, raised to 210 °C at 1 °C/min and held at this temperature for 5 min, raised to 215 °C at 1 °C/min and held at this temperature for 2 min, and then raised to 240 °C at 10 °C/min and held at this temperature for 2.5 min. Standard fatty acid methyl esters (Sigma, Saint Louis, USA) were subjected to the same conditions and the following retention times were used to identify the fatty acids. Results were expressed as percentage of total area of the identified fatty acids.

2.3. Behavioral assessments

2.3.1. Open-field test

Animals (n = 8) were placed individually in the center of a circular open-field arena (50 cm of diameter, circumference 62 cm) enclosed by matte white walls and a white floor divided into squares, as previously described by Kerr et al., 2005. The number of crossings (horizontal squares crossed) and rearings (vertical movements) were recorded for 5 min and used as measures of spontaneous locomotor activity and exploratory behavior, respectively. Briefly, locomotor activity was evaluated 2 h after the last AMPH or vehicle injection (Frey et al., 2006). The open field arena was cleaned with a 5% alcohol solution between the sessions.

2.3.2. Novel object recognition task (NORT)

This paradigm is related to the natural motivation of the animals to explore novelties, being considered an innate instinct that animals use to recognize their environment (Heldt et al., 2007). The NORT was carried out in the same open-field arena 24 h after the locomotor status observations. Recognition memory was assessed as previously described (De Lima et al., 2005): arena floor was covered with sawdust (from bedding material) during the recognition memory training and test trials. On the first day, rats were given one training trial in which they were exposed to two identical objects (A1 and A2, double Lego toys), which were positioned in two adjacent corners, 9 cm from the walls, and the rats were allowed to freely explore the objects for 10 min (training session). Testing of long-term memory (LTM) was performed 24 h after the training session. The rats (n = 8) were allowed to explore the open field for 5 min in the presence of two objects: the familiar object A and a second novel object C, which were placed at the same locations as in the training session. All objects presented similar textures, colors, and sizes, but distinctive shapes. Between trials, the objects were cleaned with a 5% alcohol solution;