Journal of Functional Foods 48 (2018) 676–681

Contents lists available at ScienceDirect

Journal of Functional Foods

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

Effects of omega-3 fatty acids and sugar on attention in the spontaneously hypertensive rat

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ARTICLE INFO

Keywords:
Attention
Cognition
Omega-3 fatty acids
Sugar
Rat

ABSTRACT

Dietary omega-3 fatty acids and sugar may potentially influence cognition. The effects of reduced omega-3 PUFA and high sugar intakes in rats on attentional functions were investigated. Two groups of rat dams and their offspring were fed either an omega-3 adequate or an omega-3 deficient diet, both with high sucrose/glucose content. A control group was fed an omega-3 adequate diet containing standard levels of sugar. The offspring were tested in a 3-choice-serial-reaction-time task. Compared to controls, statistically significant reductions in attention were found in both omega-3 adequate and omega-3 deficient diet groups, both of which were fed increased amounts of sugar. No significant differences were observed between the latter two groups. These findings demonstrate the detrimental effects of high sugar intake on attention with no exacerbation of these effects by omega-3 PUFA reduction. The interaction between dietary components should be taken into consideration when investigating the effects of nutritional modifications.

1. Introduction

Polyunsaturated fatty acids (PUFAs) have been posited to play a crucial role in neuronal development and functioning of the central nervous system (Liu, Green, John Mann, Rapoport, & Sublette, 2015; Morgese & Trabace, 2016; Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010; Wainwright, 2002). PUFAs such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid (AA) exert an influence on numerous neuronal processes, e.g. the fluidity of membranes and regulatory processes of gene expression (Jiao et al., 2014; Liu et al., 2015; Schuchardt et al., 2010; Wainwright & Huang, 2002; Wainwright, 2002). Several human studies indicate that a deficiency of omega-3 (n-3) fatty acids leads to an imbalance of the n-3/n-6 PUFA ratio, which has the potential to affect neurocognitive functions and may be associated with developmental disorders (Morgese & Trabace, 2016; Schuchardt et al., 2010; Stevens et al., 2003; Wainwright & Huang, 2002; Wainwright, 2002). A possibly impaired metabolism of PUFAs has been discussed as a potential risk factor for the development of neuropsychiatric disorders including attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (Cooper, Tye, Kuntsi, Vassos, & Asherson, 2015; Morgese & Trabace, 2016; Schuchardt et al., 2010; Wainwright & Huang, 2002). However, findings pertaining to possible therapeutic effects of dietary PUFAs in children and adolescents with such developmental disorders have been inconclusive (Hirayama, Hamazaki, & Terasawa, 2004; Morgese & Trabace, 2016; Schuchardt et al., 2010; Sorgi, Hallowell, Hutchins, & Sears, 2007; Voigt et al., 2001). Experimental animal studies have repeatedly shown that dietary supplementation with n-3 PUFAs may enhance both synaptic development and function (Cao et al., 2009; Dervola et al., 2012; Kim et al., 2011; Su, 2010). Fatty acids in neurons and glia cells may influence the properties of the cell membrane, membrane-associated proteins, gene transcription, neurotransmitter metabolism and synaptic functions (Chalon, Vancassel, Zimmer, Guilloteau, & Durand, 2001; Dervola et al., 2012; Drevon, 1992; Levant, Ozias, & Carlson, 2006).

The spontaneously hypertensive rat (SHR) is a widely accepted model of ADHD (Sagvolden, 2000; Sontag, Tucha, Walitza, & Lange, 2010) with characteristic behavioral symptoms (Hauser et al., 2014; Wainwright & Huang, 2002) and a decrease in dopaminergic function in the prefrontal cortex (Russell, Villiers, Sagvolden, Lamm, & Taljaard, 1995). The SHR has both a deficient metabolism of n-3 fatty acids and lower brain levels of n-3 PUFAs, as compared to Wistar-Kyoto (WKY) rats (Mills & Huang, 1992; Wainwright & Huang, 2002). This finding posits a central role of n-3 PUFAs in cognitive domains involved in ADHD, i.e. attentional functioning and impulse control. To address this issue and to investigate the potential beneficial effects of increased n-3 fatty acid levels in this animal model of ADHD, Dervola et al. (2012) investigated the effects of prenatal n-3 fatty acids supplementation in SHR and WKY on attention, impulsivity and motor activity. In their

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https://doi.org/10.1016/j.jff.2018.07.057
Received 3 April 2018; Received in revised form 25 July 2018; Accepted 26 July 2018
1756-4646/

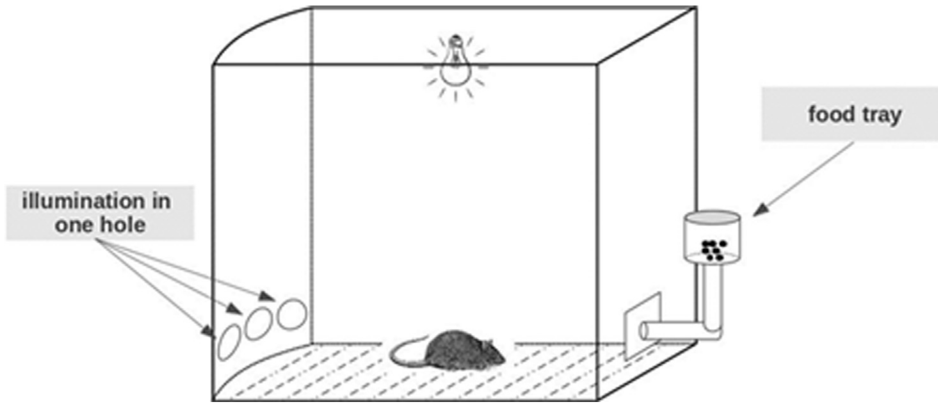

Fig. 1. Three-choice-serial-reaction-time task (3CSRTT).

study, pregnant SHR dams and their offspring were fed an n-3 PUFA enriched diet, while SHR controls were fed a control diet (ratio n-6/n-3:7/1). Post weaning, the offspring were tested for reinforcement-dependent attention, impulsivity and hyperactivity as well as spontaneous locomotion. After the behavioral testing period, animals were sacrificed and neostriatal levels of dopamine, serotonin, glutamate, and their metabolites were measured. The authors found that treatment with the n-3 PUFA enriched diet significantly enhanced attention and reduced hyperactivity and impulsiveness in male SHRs only. Both male and female SHRs showed a reduction in spontaneous locomotion when supplemented with the n-3 PUFA enriched diet. The analysis of neostriatal neurotransmitters and their metabolites showed significant changes of dopamine and serotonin in male SHRs as well as sex independent changes in glycine levels and glutamate. In light of their findings of improved reinforcement-motivated behavior in male SHRs and the improved nonreinforcement-dependent behavior in both male and female SHRs, Dervola et al. (2012) concluded that dietary n-3 PUFA supplementation has the potential to ameliorate ADHD-associated behaviors in SHRs.

Of note is the fact that the dietary conditions used by Dervola et al. (2012) varied systematically in dietary content of n-3 fatty acids and differed significantly in the amount of sucrose. The diet enriched with n-3 fatty acids contained 20% sucrose, while the control diet contained only 5.7% sucrose. The two diets differed also in the amount of other components such as total fat, cellulose, vitamin and salt mixtures (for details see Dervola et al. (2012)). Although the authors contended that the n-3 fatty acids supplementation significantly enhanced reinforcement-controlled attention and reduced lever-directed hyperactivity and impulsiveness in male SHRs (Dervola et al., 2012), these effects cannot be attributed exclusively to the changes in the amount of n-3 fatty acids, since alternative explanations involving other differences in dietary composition need to be considered.

The potential role of the consumption of mono- and disaccharides (M/D-S) in neurocognitive functioning as well as in psychiatric disorders including ADHD has been examined in a variety of animal studies. The results varied between beneficial effects of short-term M/D-S intake to impairments in cognitive functions following long-term M/D-S treatment. Some studies found beneficial effects of short-term treatment with glucose, sucrose and honey in cognitive domains such as spatial memory and other memory tasks (Chepulis, Starkey, Waas, & Molan, 2009; Lee, Graham, & Gold, 1988). In contrast, treatment with M/D-S or the consumption of a Western diet (containing high amounts of M/D-S and saturated fats) over extended periods of time may be implicated in adverse effects on memory functions, physical health and wellbeing (Cao, Lu, Lewis, & Li, 2007; Jurdak, Lichtenstein, & Kanarek, 2008; Stranahan et al., 2008). Only a small number of studies have addressed the effects of n-3 PUFA manipulation in combination with high M/D-S intake. The findings of a study by Agrawal and Gomez-Pinilla (2012) suggested that a high M/D-S diet accompanied by a reduction of n-3 PUFAs leads to a marked decline in spatial memory functions.

In the present study, we have attempted to investigate whether it is possible to impair cognitive functions of rats by administering a diet deficient in n-3 fatty acids. In addition, we have assessed the impact of a high sucrose and glucose intake in the context of experimental approaches involving the variation of dietary components such as n-3 fatty acids. For this purpose, we investigated the effects of n-3 fatty acids deficiency in a rat model for ADHD, the spontaneously hypertensive rat (SHR), by using a modified version of the 5-Choice-serial-reaction-time task, an established instrument for the assessment of attention and impulsive behavior in rodents.

2. Methods

2.1. Apparatus and testing procedure

2.1.1. Three-choice-serial-reaction-time task (3CSRTT)

The experiment was performed using four ventilated wooden chambers (Campden Instruments, Loughborough, Leicestershire, England) containing a stainless steel chamber (26 cm × 26 cm × 30 cm height). The steel chambers were lighted by 3-watt light bulbs. Each chamber was equipped with three holes, which were arranged horizontally in the curved rear wall (see Fig. 1). The holes were 2 cm above the chamber floor (stainless steel grid); each hole had a diameter of 2 cm and adjacent holes were 6 cm apart. In each hole, an infrared photocell was installed in order to detect a nose poke response of the rat to the hole. In addition, each hole was equipped with a standard light bulb (3 W). The animals were required to respond correctly to a stimulus by a nose poke into one of the three holes. A stimulus was defined as the illumination of a hole by the light bulb, and only one hole at a time could be illuminated. A correct response was rewarded with a food pellet (45 mg dustless sucrose pellets, Bio-Serv, Frenchtown, New Jersey, USA) which was dispensed into a food tray at the front wall (opposite the holes). False responses, premature responses or omissions were punished with a 5-s period of darkness.

The behavioral paradigm consisted of three phases. In the habituation phase, the ambient light was permanently turned on, 10 pellets were baited in the food tray and one pellet was placed in each illuminated hole. The rats were required to habituate to the boxes for 30 min a day. The habituation phase was finished when all pellets were found and collected, which was accomplished within two consecutive days. In the training phase, the rats were required to learn to respond correctly to the stimulus (random illumination of a hole, once per trial) in order to obtain a food pellet. The stimulus duration was gradually reduced when a rat responded correctly, within one training session of 30 min, in at least 80% of the trials (number of correct trials/total correct and false responses expressed as percent), and the omission rate was less