Brain Research Bulletin 97 (2013) 119–125

Contents lists available at SciVerse ScienceDirect

Brain Research Bulletin

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

Research report

Reduction of histamine H1 receptor binding induced by high-fat diet can be prevented by DHA and dietary fiber in specific brain areas of male rats

Zhixiang Wu[a,c], Yinghua Yu[a], Yizhen Wu[a], Craig Patch[b], Alexander Szabo[a,d], Xu-Feng Huang[a,*]

[a] Center for Translational Neuroscience, Illawarra Health and Medical Research Institute, School of Health Sciences, University of Wollongong, NSW 2522, Australia
[b] Clover Corporation Limited, Nu-Mega Ingredients Pty Ltd, NSW 2522, Australia
[c] Department of Endocrinology and Metabolism, Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, China
[d] ANSTO LifeSciences, Australian Nuclear Science and Technology Organisation, Sydney, NSW 2234, Australia

ARTICLE INFO

Article history:
Received 29 March 2013
Received in revised form 16 June 2013
Accepted 20 June 2013
Available online 28 June 2013

Keywords:
Histamine H1 receptor
Docosahexaenoic acid
Galacto-oligosaccharide
Resistant starch
Receptor autoradiography

ABSTRACT

High-fat (HF) diet and obesity are risk factors for a number of mental health problems including depression, cognitive dysfunction, dementia, and neurodegenerative diseases. Histamine H1 receptors (H1Rs) are involved in many of these conditions. This study examined H1R receptor binding density in the brain of male rats fed a high-saturated fat (HF) diet, as well as the effect of docosahexaenoic acid (DHA), galacto-oligosaccharide (GOS) and resistant starch (RS) supplementation of HF diet. Alterations of H1R expression in the post-mortem rat brain were detected by [^{3}H]-pyrilamine binding autoradiography. We found that HF diet significantly decreased H1R binding densities in the substantia nigra (SN), caudate putamen (CPu), hypothalamic arcuate nucleus (Arc), ventral tegmental area (VTA), piriform cortex (Pir) and primary motor cortex (M1), compared with low-fat fed rats, and the suppression of receptor binding density ranged from 31% to 48%. Interestingly, supplementing the HF diet with 0.5% n-3 polyunsaturated docosahexaenoic acid (DHA) prevented reduction of H1R binding densities in the SN and CPu. Addition of galacto-oligosaccharide (GOS) and resistant starch (RS) to the diet blunted HF induced reduction of H1R ligand binding in the SN and Pir, respectively. In conclusion this study showed that HF diet can alter H1R binding densities in various brain regions, and many of these changes can be prevented by adding DHA, GOS or RS to the diet.

1. Introduction

Histaminergic neurons are located in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project widely in the brain and are involved in the regulation of homeostasis, arousal, motor behavior and cognition (Haas and Panula, 2003; Masaki and Yoshimatsu, 2006; Passani et al., 2004). Histamine H1 receptor (H1R) is one of four histamine receptors belonging to the G protein coupled receptor family, and has a broad distribution in the central nervous system (Brown et al., 2001; Martinez-Mir et al., 1990). H1R regulates body energy homeostasis, cognitive function, memory, learning, sleep/wake cycle, feeding rhythms, as well as locomotor activities (Haas et al., 2008; Inoue et al., 1996; Lozeva et al., 2000).

Certain fatty acids intake can influence neuronal membrane fatty acid composition and in turn affect neurotransmitter interactions with receptors. For example, a high saturated-fat diet reduces dopamine D2 receptor density in the accumbens nucleus, striatum and hypothalamus of mice, when compared to animals fed a low-fat diet (Huang et al., 2006). We have reported that a high n-6 polyunsaturated fatty acid (PUFA) diet reduces muscarinic M2 receptor binding densities in the limbic structures of the rat brain (du Bois et al., 2005); however this is not the case for M1/M4 receptors (du Bois et al., 2006). A decreased docosahexaenoic acid (DHA, 22:6 n-3) content in brain tissue induced by α-linolenic acid-deficient diet is associated with decreased brain-derived neurotrophic factor gene expression and increased 5-HT1a receptor densities in the hippocampus of rats (Levant et al., 2008). The effect of a high saturated fat diet and DHA supplementation on the expression of H1R receptor in the brain has not been examined.

* Corresponding author at: 32.305 IHMRI, University of Wollongong, Northfield Avenue, NSW 2522, Australia. Tel.: +61 02 42214300; fax: +61 02 42214096.
E-mail address: xhuang@uow.edu.au (X.-F. Huang).

0361-9230/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brainresbull.2013.06.003

Galacto-oligosaccharide (GOS) and resistant starch (RS) are dietary fibers consumed in human diets. Both GOS and RS are fermentable fibers and can be converted to specific short-chain fatty acids in the colon. These dietary fibers have a number of beneficial health effects including reducing fat absorption, lowering blood cholesterol, stimulating the immune system, and increasing satiety (Davis et al., 2009; Higgins et al., 2001, 2005). Dietary RS increases mRNA expression of the anorexigenic protein POMC in the hypothalamus of rats (Shen et al., 2009). A recent study of ours has also shown that increasing dietary fiber intake can activate the gut-hypothalamic PYY_{3-36}-NPY, axis and increases satiety in diet-induced obese mice (Huang et al., 2011).

Histamine H1R plays an important role in numerous brain functions. A reduction in the number of H1R binding sites has been reported in elderly individuals, and during Alzheimer's disease, schizophrenia and depression (Higuchi et al., 2000; Yanai et al., 1992). It is known that a chronic high-fat diet can lead to overweight and obesity, which in turn is associated with deficits in brain function including impaired cognitive function, dementia, depression and even neurodegenerative diseases (Park et al., 2010; Winocur and Greenwood, 2005). However, the effect of high-fat diet on H1R binding density in the brain has not been examined, and therefore it is of interest to determine whether receptor expression is altered, and more importantly if changes can be prevented by manipulation of macronutrients in the diet. This study examined the effect of a high saturated-fat diet on H1R binding density in various brain regions, and also whether DHA, GOS or RS supplementation prevented high-saturated-fat diet induced alterations in H1R receptor expression in the differing brain regions.

2. Materials and methods

2.1. Animals and dietary treatments

Twenty five male Wistar rats (300–320 g) were obtained from the Animal Resources Center (Perth, Western Australia, Australia) and housed in environmentally controlled conditions (22 °C, 12 h light–dark cycle with light cycle from 06:00 to 18:00 h and dark cycle from 18:00 to 06:00 h) with ad libitum access to standard laboratory chow and water. Rats were allowed 1 week to adapt to their new environment before experiments began. They were randomized into five groups ($n = 5$): (1) standard laboratory chow as low-fat diet (LF, fat content 10% in kcal, saturated fat 1%) control, (2) high-fat (HF, 25% in kcal, saturated fat 10%), (3) HF + 5.7% GOS, (4) HF + 5.7% RS and (5) HF + 0.5% DHA. The supplement doses used in this study were based on the doses recommended for humans, including GOS at 3 g/70 kg/day, RS at 2 g/70 kg/day, and DHA at 250 mg/70 kg/day (Australian Government Food Agency Recommendations). After four weeks of dietary treatment, rats from each group were weighed and the body weight showed no statistical differences (LF: 442.5 ± 13.5 g, HF: 432.8 ± 11.1 g, HF + GOS: 439.4 ± 7.5 g, HF + RS: 453.3 ± 19.4 g, HF + DHA: 426.8 ± 8.1 g; $P = 0.599$). There was no statistical difference in average 24 h energy intake during dietary intervention (LF: 84.69 ± 1.60, HF: 94.38 ± 2.57, HF + GOS: 90.56 ± 2.19, HF + RS: 92.27 ± 2.40, HF + DHA: 90.88 ± 2.78 kcal/day, $P = 0.056$). In order to minimize the impact of circadian variation on binding density, the rats were sacrificed between 07:00 and 09:00 h by rapid CO_2 asphyxiation, and the brains were immediately removed and frozen in liquid nitrogen. The study was approved by the University of Wollongong Animal Ethics Committee and all animal experiments were conducted in compliance with the National Health and Medical Research Council Australian, Code of Practice for the Care and Use of Animals for Scientific Purposes (2004).

2.2. Histology and [^{3}H]-pyrilamine binding autoradiography

Coronal brain sections (14 μm) were cut at −18 °C with a cryotome (Clinicut Cryostat; Bright Instruments), and thaw-mounted onto poly-L-lysine coated microscope slides (Polysine™, Menzel GmbH & Co, KG) (Wang and Huang, 2008). [^{3}H]-pyrilamine autoradiography was performed following procedures as described in previous work from our laboratories and others (Han et al., 2008; Hu et al., 2010). In brief, sections were incubated at room temperature for 15 min, then incubated for 60 min in 50 nM sodium potassium phosphate buffer containing 10 nM [^{3}H]-pyrilamine (specific activity, 25.8 Ci/mmol; Perkin Elmer, Boston, MA) at room temperature. Non-specific binding was determined by addition of 10 μM triprolidine to the incubation buffer. Sections were washed in 4 °C buffer (4× 2 min), dipped in distilled water and dried.

2.3. Quantification and statistical analysis

Images were obtained using high resolution Beta Imager detection (BioSpace, Paris, France) according to the method that we have used previously (Deng and Huang, 2006; Hu et al., 2010; Huang et al., 2008). In brief, sections were placed inside the detection chamber of the Beta Imager and scanned for 3.5 h at a high-resolution setting. The levels of bound radioactivity in the brain sections were directly determined by counting the number of β-particles emerging from the tissue sections, which was followed by analysis of activity in the regions of interest using the Beta Vision Plus Program (BioSpace). Radioligand binding signals were expressed in counts per minute per square millimeter (cpm/mm^2). For quantification, linearization was done based on standards developed from sections cut from brain pastes containing a series of known amounts of radioligands. This allows the measurement of radioligand binding signals to be converted into nCi [^{3}H] ligand per mg tissue equivalent. The [^{3}H]-pyrilamine binding density in various brain regions was quantified by measuring the average density of each region in three to five adjacent brain sections including both brain hemispheres (Deng and Huang, 2006; Hu et al., 2010; Huang et al., 2008). The specific binding values were obtained by subtracting non-specific binding values from the total binding values. Brain regions were identified with reference to a standard rat brain atlas (Paxinos and Watson, 1997) (Fig. 2). The structures of both hemispheres were quantified ($n = 5$ per group). Data were analyzed statistically using the SPSS 17.0 program (SPSS, Chicago, IL, USA). Histamine H1R binding density for each brain area was analyzed by one-way ANOVA followed by a post hoc Tukey–Kramer–HSD test. Data were expressed as mean ± SEM. P values less than 0.05 were regarded as statistically significant.

3. Results

Specific binding of the H1R ligand [^{3}H]-pyrilamine was observed in most brain regions examined (Table 1 and Fig. 1). Among the various brain regions, the highest [^{3}H]-pyrilamine binding densities were observed in the arcuate hypothalamic nucleus (Arc), caudate putamen (CPu), hippocampus (Hip), medial posterodorsal amygdala (MeP), and ventromedial hypothalamic nucleus (VMH). Lower [^{3}H]-pyrilamine binding densities were observed in the substantia nigra (SN), piriform cortex (Pir), primary motor cortex (M1), ventral tegmental area (VTA), and anterior cingulate cortex (ACC). Non-specific binding of [^{3}H]-pyrilamine was less than 5%.

3.1. Effects of HF diet and GOS, RS, and DHA supplements on H1R binding density in the substantia nigra (SN)

There were significant differences in H1R binding densities in the SN among the five diet treatment groups (LF, HF, DHA, GOS and RS) after 4 weeks ($F_{4,20} = 14.11$, $P < 0.001$) (Table 1, Figs. 1A and 3). Rats on HF diet had significantly lower H1R binding density in the SN than rats on the LF diet (48%, $P < 0.001$). Addition of GOS, RS and DHA to the HF diet significantly increased SN H1R binding densities compared to animals on HF diet alone (GOS: 51%, $P = 0.028$; RS: 50%, $P = 0.036$; DHA: 105%, $P < 0.001$). Furthermore, the DHA group was more potent in increasing H1R density than either the GOS or RS groups (DHA vs. GOS: 36%, $P = 0.02$; DHA vs. RS: 37%, $P = 0.015$).

3.2. Effects of HF diet and GOS, RS, and DHA supplements on H1R binding density in the caudate putamen (CPu)

Significant differences were observed in H1R binding densities in the CPu among the five treatment groups after 4 weeks of dietary intervention ($F_{4,20} = 8.78$, $P < 0.001$) (Table 1, Figs. 1B and 4). HF diet significantly reduced H1R binding in the CPu (45%, $P < 0.001$) in comparison to the LF diet. DHA supplementation significantly increased H1R density compared to HF alone (43%, $P = 0.046$), while in the GOS and RS supplement groups binding density was not significantly different from the HF group.

3.3. Effects of HF diet and GOS, RS, and DHA supplements on H1R binding density in the piriform cortex (Pir)

We also found significant differences in H1R binding densities in the Pir among the five groups of rats after 4 weeks of dietary