Biochimie 120 (2016) 75–80

Contents lists available at ScienceDirect

Biochimie

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

Mini-review

Triglyceride sensing in the reward circuitry: A new insight in feeding behaviour regulation

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ARTICLE INFO

Article history:
Received 9 March 2015
Accepted 3 July 2015
Available online 6 July 2015

Keywords:
Obesity
Triglycerides
Feeding behaviour
Reward
Lipoprotein lipase

ABSTRACT

In both developed and emerging countries, sedentary life style and over exposition to high energy dense foods has led to a thermodynamic imbalance and consequently obesity. Obesity often involves a behavioural component in which, similar to drugs abuse, compulsive consumption of palatable food rich in lipids and sugar drives energy intake far beyond metabolic demands. The hypothalamus is one of the primary integration sites of circulating energy-related signals like leptin or ghrelin and is therefore considered as one of the main central regulators of energy balance. However, food intake is also modulated by sensory inputs, such as tastes and odours, as well as by affective or emotional states. The mesolimbic pathway is well established as a key actor of the rewarding aspect of feeding. Particularly, the hedonic and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine (DA) in striatal structure such as the Nucleus Accumbens (Nacc). In both rodent and humans several studies shows an attenuated activity of dopaminergic signal associated with obesity and there is evidence that consumption of palatable food per se leads to DA signalling alterations. Furthermore impaired cognition in obese mice is improved by selectively lowering triglycerides (TG) and intracerebroventricular administration of TG induces by itself acquisition impairment in several cognitive paradigms in normal body weight mice. Together, these observations raise the possibility that nutritional lipids, particularly TG, directly affect cognitive and reward processes by modulating the mesolimbic pathway and might contribute to the downward spiral of compulsive consumption of palatable food and obesity. This review is an attempt to capture recent evolution in the field that might point toward a direct action of nutritional lipid in the reward circuitry.

1. Introduction

Between 1980 and 2008 the mean body mass index (BMI) of the world's population has increased dramatically. Globally, in 2008, around 35% of adults aged 20 and over were overweight and around 12% were obese (World Health Organization (WHO) estimations). Maintenance of a healthy body weight is possible through a fine regulation of energy balance which coordinates energy intake and expense. The brain is a central regulator of food intake and energy balance and the hypothalamus is one of the primary sites of circulating energy-related signals integration like leptin, ghrelin, or nutrients [1]. Imbalance in this regulatory process often leads to metabolic diseases such as obesity and diabetes in both humans and rodent models [1,2]. Among circulating nutrients, detection of lipids in the hypothalamus has emerged as a key component in brain regulation of energy balance [3,4]. Alteration of hypothalamic lipid sensing appears to be involved in several brain responses to nutrient oversupply (i.e inflammation, ER stress . . .) that leads to obesity [5,6]. However, food intake is also modulated by sensory inputs, such as tastes and odours, as well as by affective or emotional states. For example, stress or anxiety can stimulate reward seeking and consumption of highly palatable food independent of metabolic demand [7]. Among several brain circuits, the mesolimbic pathway is well established as a main actor of the rewarding aspect of feeding. The hedonic and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine (DA) in striatal structure such as the Nucleus Accumbens (Nacc). DA release is stimulated by

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http://dx.doi.org/10.1016/j.biochi.2015.07.004
0300-9084/

high-fat/high-sugar (HFHS) foods as well as by various reinforcing stimuli [8–10]. HFHS diet consumption in both human and rodent has been associated with the progressive loss in spontaneous locomotor activity, and it has been shown that an acute reduction in locomotor activity is a major contributor to western diet-induced obesity in mice [11]. Moreover HFHS consumption was also linked to the establishment of an addictive-like reward dysfunction and compulsive eating in obese rats [12] and depressive like behaviour [13]. Obesity-associated cognitive impairment can be improved by selective lowering of circulating triglyceride (TG) [14]. Altogether, those observations raise the possibility that nutritional lipids, specifically in the form of circulating triglycerides, might directly act on the brain structure-through a mechanism similar to hypothalamic lipid sensing to affect cognitive and reward processes and contribute to the establishment of compulsive food consumption.

In this review, we will focus on mechanisms by which nutritional lipids might act in the brain to regulate different components of energy balance with recent evolutions in the field that point toward a direct action of triglyceride in reward seeking behaviour.

2. Central regulation of feeding behaviour

2.1. The homeostatic component of feeding: the hypothalamus pathway

Circulating signals like ghrelin or leptin reflect the energy needs of an organism and are integrated at the level of the hypothalamus. Several hypothalamic nuclei are interconnected to insure proper regulation of feeding, among which the arcuate nucleus (ARC) is well positioned close to a circumventricular organs called the median eminence (ME) that allows a privileged access to blood signals. ARC neurons can directly sense circulating factors like insulin, ghrelin, leptin or nutritional signals like glucose, amino-acids or lipids [15]. Two distinct groups of ARC neurons are directly controlling energy balance, the neurons containing orexigenic neuropeptides, agouti-gene-related protein (AgRP) and neuropeptide Y (NPY) (NPY/AgRP Neurons), and the neurons containing anorexigenic neuropeptides, pro-opiomelanocortin (POMC) and cocaine-and amphetamine-related transcript (CART) [15]. POMC neurons are activated by anorectic signals like leptin and insulin [16] and their activation decreases feeding [17,18]. Conversely, NPY/AgRP neurons are activated by orexigenic factors like ghrelin [19] and their activation stimulates food intake particularly by inhibiting POMC neurons and neurons expressing melanocortin receptors (MCR) [15]. ARC neurons project to the several secondary structures inside and outside the hypothalamus which, in turn, project to other brain areas, essential for the long-term regulation of energy homeostasis [15,20].

2.2. Hedonic & motivational aspect of feeding: a focus on the mesolimbic pathway

Hypothalamic integration of orexigenic and anorexigenic circulating signals allow the brain to adapt food intake according to energy needs, however, food palatability is an integral component of the reward associated with food. Palatability defines the properties by which food induces sensitive response and increased desire in animals [21]. Food palatability is characterized by the composition, the smell, the taste, the texture, the temperature and the appearance of the food. High proportions of lipids and/or sugar usually are found as a combination for highly palatable food composition. Nevertheless, it is not only the inherent properties of food that can have an impact: experience, metabolic demand and other environmental influences like stress are also determining factors [22].

The mesolimbic pathway is one of many neural networks which encode different aspect of food intake [9,23]. Several pharmacological interventions using DA receptor agonist and antagonist have proven the efficiency for DA signalling to interfere with energy intake. DA antagonist increases body weight whereas DA agonist leads to decrease energy intake [24,25]. DA signalling is mediated through the activation of G-protein-coupled DA receptors-D1 and D5 coupled to Gsα; D2, D3 and D4 coupled to Giα-which activate intracellular signalling pathways in postsynaptic neurons. DA neurons are mainly located in the Ventral Tegmental Area (VTA) and innervate limbic regions like the Nacc, the prefrontal cortex (PFC), the amygdala (AG) and the hippocampus (HP). Environmental stimuli perceived as salient will trigger DA release by DA neurons [8]. Palatable food ingestion leads to DA release in Nacc, and correlates with the re enforcing strengths of the stimuli [26,27]. DA is also involved in the motivation to perform behaviour tasks necessary to procure and consume the food. Animals unable to produce DA exhibit aphasia and a profound lack of goal-directed behaviour which ultimately lead to starvation and death if pharmacological rescue is not applied [28,29]. Moreover, it was found that while chemical lesions of the DA system (pharmacological antagonists of DA receptor) inhibit food-seeking behaviour it does not impact onto oro–facial reactions associated with pleasurable to intra oral sucrose delivery [30,31]. These observations led to the concept that goal-directed behaviour and actual pleasure associated with salient food stimuli could rely on a different neurochemical architecture and could be conceptually dissociated with 3 primary components termed “learning”, “liking” and “wanting”, respectively. With regard to neurochemical mediation, it was proposed that “wanting” is governed by DA whereas “liking” depends upon opioid transmission [32]. Although, DA is a neurotransmitter well studied in reward processes, opioids, endocannabinoids, serotonin and others are also involved in the rewarding aspect of food intake [33–35]. As most other studies working on mesolimbic system alterations and triglycerides are focussing on the dopaminergic circuitry we chose to describe only this system.

In summary, important components of food-associated reward are directly encoded through dopamine release however the neurochemical characterization of this process is still discussed [8,32,33,35–38].

3. Alteration of the mesolimbic pathway associated with obesity

Several studies have shown that High Fat (HF) diet consumption induces hypothalamic changes resulting in disruption of energy balance. Different processes like Endoplasmic Reticulum (ER) stress, apoptosis or synaptic remodelling were described to participate in the alteration of energy-sensing mechanism during HF feeding and obesity [6,39–44]. Particularly, nutritional lipids seem to be directly involved in hypothalamic inflammatory processes associated with obesity [5,39]. Growing evidence shows that obesity is also associated with deficits in mesolimbic pathways. In rats, striatal levels of dopamine receptor D2 (D2R) were inversely related to body weight [12] and striatal decrease of D2R achieved by virus-mediated knockdown triggered the development of addiction-like reward deficits in rats on a palatable diet [12]. Another study showed that D2R activation partly redirected HF diet induced metabolic anomalies in obesity-prone mice [45,46]. In human, striatal D2R availability was significantly lower in obese individuals and the BMI correlated negatively D2R abundance; lowest D2 values positively correlated to high BMI [47,48]. Obesity was shown to be associated with a decrease in DA binding ability in striatal structures in comparison with lean humans [49] whereas obesity was associated with a greater response to food related cues in brain regions associated with reward and motivation encoding [49–51]. This suggests a possible