Central Type-1 Cannabinoid Receptor Gene

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Different neuromodulatory systems are involved in long-term energy balance and body weight and, among these, evidence shows that the endocannabinoid system, in particular the activation of type-1 cannabinoid receptor, plays a key role.

Central Type-1 Cannabinoid Receptor Gene,Energy Homeostasis,Obesity

1. Introduction

Food intake might be considered the integration of humoral and neuronal signals processed by the nervous system for the balance of energy and of sensory cues, as well as of the motivational and emotional state of an individual. Thus, different eating behaviors are finely driven by both homeostatic and hedonic signals, whose functions may vary between individuals according to previous experiences and/or epigenetic variations [1][2][3][4][5][6][7].

Homeostatic and hedonic central circuitries are interconnected, in fact feeding behaviors are affected by brain regions classically viewed as mainly involved in homeostatic feeding; however, these are also influenced by brain corticolimbic and hedonic areas, and vice versa [8][9]. The homeostatic feeding will be terminated once the organism is repleted with energy and nutrients, while hedonic feeding might continue. An imbalance toward the hedonic aspect of feeding without restriction may provoke changes in the food intake with serious consequences on the weight gain/loss [10][11].

The hypothalamus (HYP) is the center for the integration and control of essential bodily functions, such as circadian rhythm, body temperature and plasma-osmolarity, and traditionally recognized as the main brain region regulating food intake. It regulates feeding as a function of caloric and nutritional requirements, by sensing macronutrients and through the action of circulating regulatory hormones, neuropeptides and neuromodulators, such as leptin, cholecystokinin, ghrelin, orexin/hypocretin, insulin, neuropeptide Y, and notably lipid signals like endocannabinoids [12][13][14][15]. The imbalance in hypothalamic function may provoke an altered food intake, potentially leading to eating disorders (EDs) and obesity [16][17][18].

Besides HYP, several limbic brain areas including ventral tegmental area, nucleus accumbens (NAc), amygdala, and hippocampus, as well as cortical brain regions, have also been implicated in the hedonic aspects of feeding [19][20][21].

Studies on the role played by the reward circuits in defining hedonic aspects of feeding allowed to define how common mechanisms are shared by drug abuse and food addiction [22][23][24]. Both are compulsive behavioral disorders that induce alterations in brain mechanisms underlying synaptic plasticity and energy homeostasis, showing common vulnerabilities and pathophysiological aspects [25].

Among the different neuromodulatory systems involved in long-term energy balance and body weight regulation, many preclinical and clinical evidence show the key role of the endocannabinoid system (ECS) [26], and in particular, the activation of type-1 cannabinoid receptors (CB_1R) [27][28].

Indeed, several preclinical studies show that orexigenic stimuli induce CB_1R activation in the rat brain, specifically in the HYP [29][30] where CB_1R positive neurons are present in different nuclei [31], although at low density [32], and support a role in food and energy balance [33][34][35][36]. Brain reward pathways are largely responsible for processing information related to the motivation, expectation, and pursuit of pleasurable experiences, and CB_1R signaling was reported to modulate dopaminergic signaling in the ventral tegmental area and NAc to control hedonic eating [37][38][39][40]. CB_1R signaling also plays a role in the functional activity of caudal brainstem nuclei: parabrachial nucleus, nucleus of the solitary tract, and dorsal motor nucleus of the vagus nerve. Herein, CB_1R mainly controls food preferences, e.g., digestion of fat rich palatable food [37]. Several experimental findings already pointed to CB_1R as therapeutic target to treat altered feeding behavior and obesity [30][34][41][42], due to the hyperphagic role of this receptor, and the possible exploitation of its pharmacological blockade, as recently reviewed [43]. It should be recalled that rimonabant, a CB_1R antagonist/inverse agonist [44], entered the European mass market, showing weight loss benefits but it was soon withdrawn due to the significant side effects [45]. Here, we focused mainly on the role of type-1 Cannabinoid Receptor gene (CNR1) gene, which encodes for CB_1R, and its regulation in food intake and eating behaviors.

2. CNR1 Gene in the Control of Energy Homeostasis and Obesity

Circuits in the HYP regulate appetite and energy homeostasis [46] and a key role is played by hypothalamic CB_1R signaling intertwined with the pathways of metabolic hormones. In fact, for instance, the reduced hypothalamic eCB levels are associated with appetite suppression by leptin [26], while the increased hypothalamic eCB levels are correlated with orexigenic actions of ghrelin, with the involvement of the activation of AMP-activated protein kinase and the inhibition of paraventricular neurons [47].

Using mice lacking CNR1 gene, it has been documented that eCBs actions on food intake and body weight depend on the functional expression and activity of CB_1R [48]. In this work, Cota and colleagues demonstrated that germline deletion of CNR1 in male mice resulted in a phenotype characterized by decreased body weight, reduced fat mass, and hypophagia. Moreover, the study highlighted that CNR1 mRNA is co-expressed in the HYP with neuropeptides known to modulate food intake [48].

A significantly reduction in body weight was also reported in mice, where CNR1 gene expression was selectively deleted in the HYP, after 9 weeks of viral-mediated deletion. This effect, without any changes in food intake, suggested an increase in energy expenditure [49]. Further, adult mice, in which CNR1 gene was deleted in adipocytes, resulted to be protected from diet-induced obesity and associated with metabolic alterations [50].

Again, conditional mutant mice, with CNR1 deletion in forebrain and sympathetic neurons, known to control energy balance, are resistant to diet-induced obesity and display a lean phenotype [51].

Moreover, the relevant role of CB_1R in the initiation of milk suckling in pups has been observed [52][53] and, in particular, CNR1-knock-out (KO) newborns did not ingest milk on the first day of life, significantly affecting their survival rate [53].

Furthermore, central dysregulation of CNR1 gene expression has been documented in animal models of obesity in different brain areas, implicated in both homeostatic and hedonic aspects of eating [54][55][56].

In particular, the exposure to a palatable diet resulted in tissue and sex-specific changes in the gene expression of both CB_1R and type-2 cannabinoid receptor (CB_2R) in the HYP of offspring and adults. These results clearly indicate that the maternal diet has long-term effects on the development of pups through multiple alterations of signaling homeostatic pathways that include cannabinoid receptors [56].

Gamelin and colleagues (2016) found in the hippocampus of rats, fed with High Fat Diet (HFD), an increase in the CNR1 mRNA expression compared to rats fed with standard diet. The up-regulation of hippocampal CNR1 expression was increased with exercise training combined with HFD. Indeed, chronic exercise did not appear to counteract ECS overactivation and, in fact, seems even to induce this effect independently from diet. Moreover, the authors showed that CNR1 expression in the HYP is not affected by HFD in rats [54].

It was also reported, in rats exposed to HFD, the reduction in CB_1R binding sites in extrahypothalamic brain regions and CB_1R density was related to the intake of palatable food, whereas no changes have been observed in the HYP [57]. This does not exclude transient changes in CB_1R levels or CNR1 expression over time. Indeed, a transient increase in mouse hypothalamic CB_1R density, after 3 weeks of HFD, was normalized at the end of the 20 weeks of HFD, suggesting a temporal CB_1R alteration during the development of obesity [58]. A temporal transcriptional regulation of CNR1 gene was also proved in the HYP of rats exposed to diet-induced obesity. The analysis of ECS components gene expression revealed a significant and selective increase in CNR1 mRNA levels at the beginning of obesity development (5 weeks on HFD) as well as after 21 weeks of exposure, when the phenotype was already well-established. Moreover, a consistent selective and significant reduction in DNA methylation at specific Cytosine–phosphate–Guanine (CpG) sites of CNR1 gene promoter in overweight rats was observed just after 5 weeks, but not 21 weeks on HFD [55].

In the same study, the DNA methylation status of CNR1 gene was assessed in peripheral blood mononuclear cells from a subset of obese human subjects. An age-based stratification of DNA methylation levels showed a significant

reduction of the epigenetic hallmark at CNR1 promoter in younger (<30 years old) humans with obesity, when compared to age-matching controls. These findings suggest that the regulation of CNR1 gene is altered mainly at early life stage of phenotype development [55].

Considering other epigenetic modifications possibly occurring in the development of obesity, recently a hypothalamic increase in histone acetylation was reported at CNR1 gene promoter and was linked to increased receptor expression [59]. Almeida and colleagues hypothesized that maternal fat enriched diet would up-regulate CNR1 mRNA levels in the HYP of the male offspring at birth [59].

These latter findings support the relevance of environment and lifestyle in the facilitation of diseases progression, including obesity, by engaging epigenetic mechanisms [60], and in meantime could represent an innovative field to produce new strategies of intervention.

Genetic studies have identified several polymorphisms at different locations across the CNR1 gene that have been associated with obesity and related phenotypes, such as metabolic syndrome and dyslipidemia [61][62][63][64][65][66][67][68][69].

Among others, particular attention has been focused on a silent intragenic biallelic polymorphism in codon 435 of CNR1 gene, substitution of G to A at nucleotide position 1359 (1359 G/A rs1049353) [70]. This Single Nucleotide Polymorphism (SNP) was reported to be associated with abdominal adiposity [71], Body Mass Index (BMI) [72], intermuscular fat mass [73], and longitudinal changes from healthy to metabolic syndrome occurrence [74]. However, the literature has been inconsistent with respect to CNR1 polymorphisms and obesity-related markers, with many studies not finding any relevant association with CNR1 gene variants [75][76][77].

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