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Unraveling the obesity of OLETF rats

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Abstract

Cholecystokinin (CCK) is a brain gut peptide that plays an important role in satiety. CCK inhibits food intake by reducing meal size. CCK's satiety actions are mediating through its interaction with CCK1 receptors. Otsuka Long Evans Tokushima Fatty (OLETF) rats are a CCK1 receptor knockout model that allows the study of multiple CCK functions. OLETF rats are hyperphagic with the hyperphagia expressed as a significant increase in the size of meals. OLETF rat obesity is secondary to the hyperphagia and has been proposed to derive from two regulatory deficits. One is secondary to the loss of a feedback satiety signal. The other results from increased dorsomedial hypothalamic NPY expression. Recent studies have examined developmental aspects of altered feeding, body weight and orexigenic signaling in OLETF rats. OLETF rats demonstrate increases in meal size in independent ingestion tests as early as two days of age. OLETF pups are also more efficient in suckling situations. Consistent with such developmental differences, examinations of patterns of hypothalamic gene expression in OLETF pups indicate significant increases in DMH NPY expression as early as postnatal day 15. Access to a running wheel and the resulting exercise have age dependent effects on OLETF food intake and obesity. With running wheel access shortly after weaning, food intake decreases to the levels of LETO controls. When running wheel access is discontinued, food intake temporarily increases resulting in an intermediate phenotype and the absence of diabetes. Together these data demonstrate roles for peripheral CCK and CCK in feeding and body weight control and support the use of the OLETF rat as a model for examining obesity development and for investigating how interventions at critical developmental time points can alter genetic influences on food intake and body weight.

Keywords: Satiety; DMH; NPY; Exercise

1. Introduction

Genetic obesity models have the potential to identify a range of factors that contribute to obesity development. Rodent models were instrumental in the identification of leptin, the adiposity signal that is a major influence on energy balance. Ob/ob mice lacking leptin were first identified in the 1970s but it was not until the mid 1990s that leptin was identified as the missing protein that led to obesity in this model [1]. The identification of leptin greatly advanced our understanding of hypothalamic systems involved in energy balance. Leptin's major site of action is the hypothalamic arcuate nucleus where leptin interacts with two distinct neuronal subtypes, one containing the orexigenic peptides neuropeptide Y (NPY) and agouti related peptide (AgRP), and the other containing the prepropeptide, proopiomelanocrtin (POMC), that produces the anorexigenic peptide alpha melanocyte stimulating hormone (α-MSH) [2]. A variety of obesity models have now been identified that involve defects in aspects of the leptin signaling pathway and its downstream mediators [3–6]. Other rodent obesity models that do not derive from deficits in the leptin signaling pathway have also been identified. This review will focus on one such model, the OLETF rat and how study of this model and its metabolic and behavioral deficits have identified novel actions of hypothalamic signaling in the controls of food intake and developmental events that contribute to overall energy balance.

2. OLETF rats

In response to the appearance of a spontaneous obesity in an outbred colony of Long Evans rats, Otsuka Pharmaceuticals

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developed two lines of rats by selective breeding. These are now referred to as the obese Otsuka Long Evans Tokushima Fatty (OLETF) and the control Long Evans Tokushima Otsuka (LETO) [7]. OLETF rats were initially characterized as having late onset hyperglycemia, polyuria, polydipsia and mild obesity and were studied as a model of non insulin dependent diabetes mellitus (NIDDM — type II diabetes) [7].

OLETF rats are hyperphagic, consuming roughly 30% more than LETO controls. They become obese, with male and female OLETF rats demonstrating different weight trajectories compared to LETO controls. Ten week old male OLETF rats weigh 25–30% more than LETO controls and at this age the difference in female rats is less. With aging, the degree of obesity in male rats peaks at about 35% while it increases beyond that in females (LETO males eventual become obese lessening the difference between OLETF and LETO rats while LETO females do not become obese). The OLETF rat differs from other rat obesity models in that their fat deposition is predominately intra-abdominal or visceral. In other models such as the Zucker rat, fat deposition is predominately subcutaneous [8]. OLETF rats have impaired glucose tolerance by 5 weeks of age, a time point at which there is not a reliable increase in body weight compared to LETO controls. With age, the degree of glucose intolerance increases and both male and female OLETF rats become clearly hyperglycemic and hyperinsulinemic. A significant proportion of male OLETF rats eventually develop insulin dependent diabetes [7].

Studies characterizing overall pancreatic function in the OLETF rat initially demonstrated the absence of a pancreatic acinar cell response to the brain/gut peptide cholecystokinin (CCK) [9]. This lack of a response to CCK led to investigations of CCK receptor distribution and function in the OLETF rat, resulting in the detection of an absence of CCK-1 receptor gene expression. Southern blot analysis failed to show a restriction band consistent with the CCK-1 receptor gene in OLETF rats and cloning and sequencing of the CCK-1 receptor gene in the OLETF rat identified a 6847 base pair deletion in the gene that spanned the promoter region and the first and second exons [10]. This deletion and its accompanying disruption of CCK-1 receptor protein production make the OLETF rat a naturally occurring CCK-1 receptor knockout model.

3. CCK and CCK-A receptors in food intake control

CCK is a brain/gut peptide that is released from the proximal intestine in response to the intraluminal presence of nutrient digestive products [11]. Endogenously released CCK plays a variety of roles in modulating overall digestive function. It slows gastric emptying, stimulates pancreatic and gall bladder secretion and modulates intestinal motility [12]. CCK has also been shown to play a role in satiety. Exogenous peripheral administration of CCK reduces food intake and results in the earlier appearance of satiety [13]. CCK's actions are specific to meal size. Meal contingent administration of CCK in rats produces consistent reductions in the size of meals without altering total food intake [14]. Meal frequency increases to compensate for the decrease in meal size. The actions of exogenous CCK mimic those of the endogenous peptide. Administration of CCK antagonists result in increases in meal size and, in the sort term, increases in food intake [15,16]. The feeding inhibitory actions of CCK are peripherally mediated with major sites of action being the afferent vagus [17] and the circular muscle layer of the pyloric sphincter [18].

CCK's feeding inhibitory actions are mediated through interactions with CCK-A receptors. Two CCK receptor subtypes have been identified. These were originally pharmacologically characterized based on differential affinities of various CCK binding sites for various CCK fragments and analogs [19]. Two G protein coupled CCK receptor proteins have now been identified and the genes responsible for their expression have been sequenced [20,21]. The distribution of CCK receptors is species specific. In rat, CCK-A (now referred to as CCK-1) receptors are expressed in the pancreas, pyloric sphincter, vagal afferent cell bodies in the nodose ganglion and in a limited number of brain sites [19,22]. CCK-B receptors (now referred to as CCK-2 receptors) are found in stomach, intestine, nodose ganglion and are widely distributed throughout the brain [19,22]. Work with CCK receptor antagonists with relative specificity for one or the other receptor subtype has demonstrated that the feeding inhibitory actions of both exogenous and endogenous CCK with depends upon of CCK-1 but not CCK-2 receptor interactions [16,23].

4. Disordered food intake in OLETF rats

OLETF rats lacking CCK-1 receptors are insensitive to the feeding inhibitory actions of exogenous CCK [24]. Meal pattern analyses from tests in which rats had 24 hour access to 45 mg food pellets demonstrated specific alterations in meal size in OLETF rats [24]. As shown in Fig. 1, OLETF rats had almost twice the average meal size of LETO controls. In response to this increase in the size of their spontaneous meals, meal frequency decreased but not sufficiently to compensate for the increase in meal size, resulting in a relative overall hyperphagia. Analysis of the microstructure of consuming liquid nutrients reached similar conclusions — increased durations of drinking consistent with impaired satiety without changes in the initial rates of consumption [24]. The role of the increased food intake in the obesity of the OLETF rat was evaluated in pair feeding studies in which one group of OLETF rats were fed the amounts consumed by ad lib fed LETO rats. As demonstrated in Fig. 2, pair feeding completely prevented the OLETF obesity leading to the conclusion that the obesity is secondary to the increased food intake [25]. Importantly, pair feeding also normalized fat pad weight, and plasma glucose and insulin levels in OLETF rats, further highlighting the role of the increased food consumption in the obesity and diabetes of OLETF rats [25].

OLETF rats have also been demonstrated to overconsume both dietary fat and sweetened foods. Consistent with a role for peripheral endogenous CCK in mediating the satiating effects of fatty foods, OLETF rats have a deficit in satiety for fatty foods. They decrease their food intake less than LETO control rats in response to gastric or intestinal lipid infusions [26]. Furthermore, OLETF rats overconsume high fat diets to a greater