European Journal of Pharmacology 660 (2011) 28–42

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Review

Neurobiology of overeating and obesity: The role of melanocortins and beyond

Rahul Pandit [a,*], Johannes W. de Jong [a], Louk J.M.J. Vanderschuren [a,b], Roger A.H. Adan [a]

[a] Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands
[b] Department of Animals in Science and Society, Division of Behavioural Neuroscience, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 2, 3584 CM Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 28 September 2010
Received in revised form 10 January 2011
Accepted 13 January 2011
Available online 2 February 2011

Keywords:
Obesity
Leptin resistance
Addiction
Craving
Melanocortin

ABSTRACT

The alarming increase in the incidence of obesity and obesity-associated disorders makes the etiology of obesity a widely studied topic today. As opposed to 'homeostatic feeding', where food intake is restricted to satisfy one's biological needs, the term 'non-homeostatic' feeding refers to eating for pleasure or the trend to over-consume (palatable) food. Overconsumption is considered a crucial factor in the development of obesity. Exaggerated consumption of (palatable) food, coupled to a loss of control over food intake despite awareness of its negative consequences, suggests that overeating may be a form of addiction. At a molecular level, insulin and leptin resistance are hallmarks of obesity. In this review, we specifically address the question how leptin resistance contributes to enhanced craving for (palatable) food. Since dopamine is a key player in the motivation for food, the interconnection between dopamine, leptin and neuropeptides related to feeding will be discussed. Understanding the mechanisms by which these neuropeptidergic systems hijack the homeostatic feeding mechanisms, thus leading to overeating and obesity is the primary aim of this review. The melanocortin system, one of the crucial neuropeptidergic systems modulating feeding behavior will be extensively discussed. The inter-relationship between neuronal populations in the arcuate nucleus and other areas regulating energy homeostasis (lateral hypothalamus, paraventricular nucleus, ventromedial hypothalamus etc.) and reward circuitry (the ventral tegmental area and nucleus accumbens) will be evaluated and scrutinized.

Contents

1. Introduction

The rapid urbanization throughout the globe in the past few decades, marks the rise in the incidence of many chronic illnesses, including obesity and diabetes (Fry and Finley, 2005). Recent data from Europe and The United States shows a high incidence of obesity in the general population, 20% and 34%, respectively (Fry and Finley, 2005; Nguyen and El-Serag, 2010). Interestingly, only in an insignificant subset, obesity is a result of single mutation in genes involving energy homeostasis. A majority of cases of obesity results from a combination of genetic, behavioral and environmental factors. The

* Corresponding author.
E-mail address: rpandit15@gmail.com (R. Pandit).

0014-2999/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2011.01.034

improvements in food availability and alterations in dietary patterns with a prevalence of energy-dense fat and sweet foods are crucial environmental factors in today's obesity epidemic. Distinguished from 'homeostatic feeding', where food intake is restricted to satisfy one's biological needs, this kind of 'non-homeostatic feeding' or 'feeding for pleasure' has gained a special place in our society and overeating, food craving and compulsive eating are important deleterious factors culminating in obesity.

The increased attraction towards pleasurable feeding and the loss of control over food intake have been compared to addictive behavior. Studies on animals and humans have demonstrated activation of the brain reward system when subjects are exposed to palatable food. Thus, homeostatic control of feeding, where the brain maintains a temporal control on the amounts of food ingested involves the hypothalamus and the brainstem, whereas the reward circuit, encompassing brain areas such as the ventral striatum, prefrontal cortex and amygdala is sensitive to the hedonic aspects of food. Interestingly, the systems involved in homeostatic and non-homeostatic feeding are not entirely separated, as multiple connections between these two systems exist (Lutter and Nestler, 2009). Additionally, in a situation of hunger even non-palatable foods will be rewarding. This suggests the existence of a distributed neural network that controls different aspects of feeding behavior, with rostral limbic and cortical brain areas being more important for pleasure feeling and caudal parts for controlling meal size (Adan et al, 2008). Overconsumption in this paper will be studied in the light of two contributing factors: (a) increase in meal size, i.e. animals consume bigger amounts of food due to defective satiation and/or augmented desire for certain foods (Fulton, 2010) and (b) increase in meal frequency. We aim to understand the neural mechanisms by which the hedonic signals interact and hijack the homeostatic regulation of food intake. Although at first glance, hijacking of the homeostatic regulatory mechanisms by its hedonic counterpart may seem conflicting, it should be borne in mind that during evolution, humans have lived in an environment where food availability was restricted and uncertain (e.g. hunter–gatherers) and the biological system has been 'hard-wired' to maximize energy stores (Schwartz et al, 2003).

2. Homeostatic control of food intake

The question concerning the regulation of food intake has intrigued scientists for several decades. The actual shift from the earlier 'peripheral' theories, where hunger and satiation were considered to be a unique property of the stomach, to the more 'central' theories, involving the brain in feeding control, did not occur until the 1950s. Correspondingly, the glucostat theory of Mayer and the lipostat theory of Kennedy suggested the role of carbohydrate and fat as major components regulating energy balance (Kennedy, 1953; Mayer, 1955). Lesion experiments during this period also identified the ventromedial hypothalamus and the lateral hypothalamus as the brain 'satiety' and 'feeding' center, respectively (Mayer and Thomas, 1967). These observations, although somewhat preliminary, laid the foundation for further elucidation of the complex neuronal networks influencing feeding and satiation. A major breakthrough in obesity research came through studying spontaneously obese mice, the ob/ob (obese) and the db/db (diabetic) mice being the forerunners (Speakman et al., 2007). Using surgical vascular-anastomosis between these strains and normal mice, it was shown that the ob/ob and the db/db mice had a dysfunctional 'satiety factor' and 'satiety center', respectively (Coleman, 1973). Later, with the advent of better molecular cloning techniques, this satiety factor was identified in 1994 as circulating leptin, which appeared to be absent in the ob/ob mouse, while a dysfunctional long form of leptin receptor (see below) was identified as the cause of obesity in the db/db mouse (Zhang et al., 1994; Tartaglia et al., 1995).

Leptin is perhaps the most widely studied biological factor controlling food intake. Secreted primarily from the adipose tissue, leptin is a 146 amino acid protein circulating in the blood. It accomplishes a biochemical communication between adipose tissue and the brain areas involved in energy homeostasis, updating the latter on the degree of peripheral adiposity (Margetic et al., 2002). The action of leptin in the brain is mediated by the leptin receptor, which belongs to the class-I cytokine receptor family (Tartaglia, 1997). Three principal forms of leptin-receptor have been found in mammals: the secreted (leptin receptor-c), the long (leptin receptor-b) and short intracellular domain (leptin receptor-a) leptin receptor. Each carries the same extracellular domain but differs in the length of the cytoplasmic domain (Myers et al., 2008; Ahima and Osei, 2004). The leptin receptor-b is vital for the physiological action of leptin in the hypothalamus. The arcuate nucleus, dorsomedial hypothalamus, ventromedial hypothalamus and lateral hypothalamus express this form of leptin receptor (Elmquist et al., 1998). Similar to other cytokine receptors, the leptin receptor lacks an intrinsic enzymatic activity and is dependent on the Jak-2 kinases for signal transduction. Fig. 1 indicates the principal components of the leptin-signaling pathway.

2.1. Leptin resistance

The amount of circulating leptin is proportional to the degree of peripheral adiposity (Considine et al., 1996). Intriguingly, enhanced (and prolonged) increase in the circulating levels of leptin, does not further enhance the leptin receptor-b signaling cascade (Myers et al., 2008). Analogous to the concept of insulin resistance, where augmented amounts of insulin fail to decrease plasma glucose levels, leptin resistance implies a clinical condition associated with obesity, where the anorectic action of leptin is blunted despite its high circulating amounts in the periphery (Munzberg et al., 2005).

Being one of the central issues in understanding obesity, several explanations have been put forward to explain the phenomenon of leptin resistance. First, studies comparing the db/db mouse, which lacks only leptin receptor-b and mouse mutants devoid of all isoforms of leptin receptor, showed that the soluble and short isoforms of leptin receptor may be responsible for leptin's transport across the blood brain barrier (Shimizu et al., 2007). Deficiencies in the peripheral levels of these isoforms in obese conditions indicate their potential role in leptin resistance (Ogier et al., 2002). Second, the inability of leptin to reach its target can be also due to other factors, like the high levels of circulating triglycerides in obesity, which hinder leptin transport across the blood brain barrier (Banks et al., 2004). Third, intracellular mechanisms activated by the leptin signaling cascade also modulate the action of leptin receptor by negatively regulating its own receptor activity. One such mechanism is suppressor of cytokine signaling-3 (SOCS-3) activation. Signal transducer activator of transcription-3 (STAT-3) protein activated upon phosphorylation of leptin receptor-b, further activates SOCS-3 protein, which in turn suppresses the activity of the leptin receptor by acting at the level of Jak-2 kinase and Tyr 985 residue of the leptin receptor. Neuronal SOCS-3 deficient mice show enhanced STAT-3 protein phosphorylation together with a leaner phenotype (Mori et al., 2004). Focusing on the dose-related effect of leptin on its receptor to explain leptin resistance, Munzberg et al. (2005) hypothesized that under baseline levels, small increments in leptin concentrations would result in enhancement of leptin signaling, whereas elevated amounts of leptin as encountered in obesity, would lead to higher expression of SOCS-3, thereby dampening leptin signaling. The increase of SOCS-3 expression in obesity may also occur irrespective of blunted STAT3 activation, indicating the involvement of an alternative pathway (Tups, 2009). Lastly, the tyrosine phosphatase protein 1B has shown to negatively regulate the activity of the Jak-2 kinase (Cheng et al., 2002; Zabolotny et al., 2002). Single nucleotide polymorphisms (SNP) in the gene have been associated with obesity and diabetes mellitus type II (Bento et al., 2004; Cheyssac et al., 2006). Thus, current evidence indicates the involvement of multiple simultaneous