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Review

The contribution of brain reward circuits to the obesity epidemic

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ABSTRACT

One of the defining characteristics of the research of Ann E. Kelley was her recognition that the neuroscience underlying basic learning and motivation processes also shed significant light upon mechanisms underlying drug addiction and maladaptive eating patterns. In this review, we examine the parallels that exist in the neural pathways that process both food and drug reward, as determined by recent studies in animal models and human neuroimaging experiments. We discuss contemporary research that suggests that hyperphagia leading to obesity is associated with substantial neurochemical changes in the brain. These findings verify the relevance of reward pathways for promoting consumption of palatable, calorically dense foods, and lead to the important question of whether changes in reward circuitry in response to intake of such foods serve a causal role in the development and maintenance of some cases of obesity. Finally, we discuss the potential value for future studies at the intersection of the obesity epidemic and the neuroscience of motivation, as well as the potential concerns that arise from viewing excessive food intake as an "addiction". We suggest that it might be more useful to focus on overeating that results in frank obesity, and multiple health, interpersonal, and occupational negative consequences as a form of food "abuse".

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1. Introduction

One of the most alarming public health threats during the past 50 years is the increased prevalence of obesity. According to reports from the Centers for Disease Control, during the past three decades the average prevalence of obesity in the US adult population has

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risen from below 20% to 35.7% (CDC, 2012). During the same period, childhood obesity has tripled to a rate of 17%. Currently, more than 1/3 of all children and adolescents are overweight or obese. This high prevalence appears to have plateaued in the United States (Flegal et al., 2012; Ogden et al., 2012), and continues to be a major public health concern: the collective medical costs of obesity within the United States were estimated at $147 billion in 2008 (Finkelstein et al., 2009), and continue to increase with the rising cost of health care. Obesity has become a global phenomenon; the World Health Organization estimates that obesity is responsible for up to 8% of health costs in Europe and over 10% of deaths (WHO, 2012).

Obesity is a multifaceted problem, and its rapid increase in societies such as the U.S. is likely to have been brought about by several causes, both physiological and environmental. There has been a substantial change in the food environment over the past half century. In developed nations, the availability of palatable foods that are high in sugar, fat, and calories has transformed the modern food environment into one of abundance. Until the development of modern agricultural practices, food resources have been historically scarce, and thus human physiology evolved in an environment in which significant resources were required to forage for and consume sufficient calories. Physical activity also declined during this period, contributing to obesity. Across vertebrate species, central nervous system control of energy homeostasis includes behavioral regulation by hypothalamic neural circuits that monitor energy balance based upon peripheral endocrine and metabolic signals, and that serve to motivate us to seek food when energy resources are depleted. A subset of this circuitry, including that connected with the mesolimbic dopamine pathway, processes the hedonic and rewarding aspects of food and can promote the predisposition to overeat when presented with palatable and energy dense food sources. Food serves as a strong reinforcer, whether evaluated in controlled behavioral paradigms in the laboratory, or in naturalistic or societal circumstances.

The reinforcing attributes of drugs have always been, either explicitly or implicitly, linked to the reinforcement circuitry that serves to shape and select behavior based upon more natural (or physiologically relevant) rewards such as food, water, and sex. The early use of brain stimulation reward techniques and agents of abuse such as amphetamine in research both targeted and aided understanding of the neural pathways and mechanisms involved in positive reinforcement, broadly defined (e.g., Olds et al., 1971; Phillips and Fibiger, 1973). Subsequent research, including that from the laboratory of Ann E. Kelley, demonstrated that the motivational circuitry that drugs of abuse act upon serves important and distinct roles in regulating the learning and motivation underlying natural reinforcement, particularly food. In two memorable reviews, Dr. Kelley emphasized the insight that basic neuroscience research into the mechanisms of reward (Kelley and Berridge, 2002) and learning and memory (Kelley, 2004) provided in terms of understanding the processes and neural substrates that regulate adaptive behavior, and which are often driven in maladaptive ways by exposure to drugs of abuse and to the current food environment. Her scientific approach of examining the neural pathways, neurotransmitters, and molecular processes underlying learning and food motivation (reviewed elsewhere in this issue; see Andrzejewski et al., Baldo et al.) anticipated the work of many contemporary researchers interested in food and drug motivation and the intersection between the two topics.

Recently, it has been suggested that excessive intake of palatable foods may be a problem akin to that of drug addiction. Although overeating is not a psychiatric disorder, like anorexia nervosa or bulimia nervosa, it represents consistently elevated non-homeostatic feeding. The apparent parallels that might be drawn between drug and food intake as "addictive" behaviors may lie, to some extent, in the overlapping neural circuitry that is engaged by both types of motivated behaviors. However, the fact that drugs of abuse activate reinforcement circuitry involved in feeding behavior is not sufficient evidence to deduce that excessive intake of high-calorie palatable food is therefore akin to a "food addiction". For such an argument to be made, there must first be agreement upon what qualifies as an addiction, and evidence must be provided that the "addictive" intake of food parallels the behavioral patterns and physiological processes of other addictive behaviors.

The main goal of this review will be to provide a brief overview of recent research demonstrating the overlap between brain reward/reinforcement circuits as they relate to food- and drug-motivated behavior. Evidence from studies with both humans and animals will be examined. First, we will discuss the interplay between metabolic signals that monitor energy balance and the motivational circuitry that regulates the rewarding value of food and drug reinforcement. We will then discuss the ways in which food and drugs of abuse activate similar neural pathways and affect motivated behavior, how reward/reinforcement circuitry is changed by drug use or the consumption of energy dense foods, as well as how the brain responds differently to food or drugs of abuse. Finally, we will discuss the implications from this literature review regarding the heuristic value of invoking an addiction process as it relates to overeating and obesity, including the potential insights from viewing overeating patterns as an "addiction", as well as the challenges/problems/social concerns that arise from such a characterization. We suggest instead that it might be more useful to consider overeating that results in multiple negative health, interpersonal, and occupational consequences as "food abuse".

2. From motivation to action: metabolic influences on reward circuits

That the mesolimbic dopaminergic pathway is involved in the reinforcing and addictive properties of drugs of abuse has been well documented ever since Roberts et al. (1977) reported that catecholaminergic lesions of the nucleus accumbens reduced self-administration of cocaine in a rodent model. As reviewed below, both the human and rodent literature is replete with examples of how the dopaminergic and opioid systems within the substantia nigra, ventral tegmentum, and their projections to the striatum are affected by drugs of abuse. Natural reinforcers also affect behavior through these same pathways (e.g., Kelley et al., 2005a; Mogenson et al., 1980; Figlewicz Lattemann et al., 2009). Despite this understanding, it is only recently that food, and hyperpalatable foods in particular, have been posited to be potentially "addictive". This may in part be due to the fact that many early researchers interested in obesity focused upon the dysregulation of metabolic processes that result from gaining excess weight. Obesity is a complex metabolic syndrome that is characterized by energy dyshomeostasis and involves not only the brain, but also basic biochemical reactions within liver, fat, and muscle tissue. Early lines of research evolved, from the 1970s forward, that considered energy homeostasis—the regulation of feeding and regulation of body weight as a separate CNS-regulated function from appetitive motivation. However, there has always been evidence that such a dichotomy between metabolic regulation and motivated behavior might be overly simplistic. In 1962, Margules and Olds observed that both feeding and self-stimulation could be induced by electrical stimulation of identical sites within the lateral hypothalamus (LH); self-stimulation is a paradigm by which an animal presses a lever and receives a small, direct electrical stimulation of the site into which a probe is implanted. The LH was identified as a major target for self-stimulation activity and it was concluded that it was part of intrinsic 'reward circuitry' within the brain. Subsequently, Hoebel (1976)