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Comparing the effects of food restriction and overeating on brain reward systems

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ABSTRACT

Both caloric restriction and overeating have been shown to affect neural processes associated with reinforcement. Both preclinical and some clinical studies have provided evidence that food restriction may increase reward sensitivity, and while there are mixed findings regarding the effects of overeating on reward sensitivity, there is strong evidence linking this behavior with changes in reward-related brain regions. Evidence of these changes comes in part from findings that show that such eating patterns are associated with increased drug use. The data discussed here regarding the differential effects of various eating patterns on reward systems may be particularly relevant to the aging population, as this population has been shown to exhibit altered reward sensitivity and decreased caloric consumption. Moreover, members of this population appear to be increasingly affected by the current obesity epidemic. Food, like alcohol or drugs, can stimulate its own consumption and produce similar neurochemical changes in the brain. Age-related loss of appetite, decreased eating, and caloric restriction are hypothesized to be associated with changes in the prevalence of substance misuse, abuse, and dependence seen in this cohort.

1. Introduction

A unique situation is emerging among the aging population. Although caloric consumption has been shown to significantly decrease with age (Briefel et al., 1995), obesity is on the rise among members of this cohort (Salihu et al., 2009). Patterns of over- and under eating may have deleterious consequences on both the neurochemistry and behaviors associated with reward and reinforcement of behavior. Of particular relevance is the prediction that by the year 2020 the number of individuals over the age of 50 with substance abuse disorder will be two times higher than estimates from each year between 2002 and 2006 (Han et al., 2009). This prediction highlights the importance of better understanding behaviors, such as under- and overeating, which are known to cause alterations in brain reward functioning and therefore may contribute to the pathology of substance abuse.

Both preclinical and some clinical studies suggest that prolonged food restriction leads to heightened reward sensitivity (Carr, 2002; Frank et al., 2005; Frank et al., 2012). Studies examining the effects of overeating on reward sensitivity are mixed, and several theories have been developed to explain what appear to be conflicting findings (Verbeken et al., 2012). Before discussing the effects of food deprivation or overeating on reward sensitivity, however, it is important to review the neural components associated with responses to reinforcing and rewarding stimuli. Although the brain reward system is complex and consists of a number of different components (i.e., opioids, GABA), this paper will primarily review clinical and preclinical studies investigating the effects of differential feeding behavior on dopamine (DA). Mesolimbic DA neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and dopamine is considered to play an important role in influencing motivation for and the reinforcing and rewarding experiences of food consumption, drug use, and other stimuli (Everitt and Robbins, 2005; Schultz, 2010).

By studying the effects of food deprivation and overeating, it may be possible to gain a clearer understanding of the mechanisms that underlie changes in reward response or functioning due to non-homeostatic eating behaviors. In addition, by reviewing findings of studies using laboratory animal models, we may be able to gain insight into the associated biological factors without the psychological variables that may accompany aberrant eating behaviors.

2. Effects of food deprivation on reward sensitivity

2.1. Laboratory animal studies

When laboratory animals are food restricted, they show alterations in behavior that suggest increased reward sensitivity. Rats that have been even acutely food deprived exhibit higher rates of intravenous self-administration of drugs of abuse, such as cocaine and phencyclidine (Carroll et al., 1981). Further, chronic food restriction,

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accompanied by weight loss, has been shown to decrease the amount of drug necessary to experience its rewarding effects. For example, lateral hypothalamic intracranial self-stimulation (LHSS) threshold reduction has been reported in chronically food-restricted rats, suggesting lower levels of tolerance to the effects of drugs (Cabeza de Vaca and Carr, 1998). In addition to drugs of abuse, chronically food deprived and underweight animals show increased sensitivity to other, non-drug reinforcers, such as running (Pierce et al., 1986).

Additionally, there is evidence of alterations in the mesolimbic DA system that are concomitant with the behaviors noted above. Rats with a brief history of food restriction show an increase in dialysate DA in the NAc when given food that persists even after repeated exposure to a food, an effect that is not seen among non-food deprived animals (Bassareo and Di Chiara, 1999). Further, rats with restricted food access, decreased body weight, and increased exercise show higher DA release in the NAc when eating (Verhagen et al., 2009). Rats that have been chronically food deprived and are thus underweight also show approximately three times greater extracellular DA levels compared to controls when administered amphetamine in the Nac (Pothos, 2001). Increased D2 receptor availability has been found in both obese and lean rats following a prolonged period of food restriction, suggesting that the effects of food deprivation may be independent of body weight, however, less D2 receptor availability was reported in rats following an acute (24 h) period of food restriction compared to rats without food restriction, suggesting an important distinction between chronic versus acute food deprivation (Thanos et al., 2008). Compared to normal weight rats with a history of brief food deprivation, food deprived rats at 75% of their normal body weight demonstrated increased responding for oral administration of the opiate etonitazene (Carroll and Meisch, 1980). While it can be difficult to discriminate between the effects of the length of food deprivation and body weight status, as these two often coincide, it appears that these variables significantly influence alterations in reward sensitivity.

2.2. Human studies

The study of food restriction in humans may be less straightforward due to certain confounds. For example, populations who are chronically food restricted may have comorbid mental health (e.g., eating disorders) or medical issues (e.g., osteoporosis) (Dirks and Leeuwenburgh, 2006), so findings must be interpreted with caution. While these results have not been universally supported, several studies suggest that sensitivity to reward may be increased following food deprivation in humans (see review (Holsen et al., 2012)). For example, when a food reward (sucrose) was administered unexpectedly, individuals diagnosed with anorexia nervosa showed significantly greater activation in the orbitofrontal cortex (OFC), an area of the brain associated with reward or value (Peters and Buchel, 2010), compared to controls, whereas obese participants showed significantly less activation in this region compared to controls (Frank et al., 2012). This finding supports the idea that food may be especially reinforcing in food-restricted individuals.

Interestingly, when comparing reward-related brain areas of participants when hungry and when sated, Siep et al. (2009) found that when hungry, participants showed a more pronounced activation of the insula, lateral and medial OFC, caudate putamen, cingulate cortex and fusiform gyrus when presented with images of high-calorie versus low-calorie foods. This finding suggests that even a brief period of food restriction may predispose individuals to desire more calorically dense foods. Conversely, subjects showed a more pronounced response to lower calorie foods when sated (Siep et al., 2009). Similar findings have been reported within a sample of participants with obesity, suggesting that this effect may occur independent of body weight (Goldstone et al., 2009).

Similar to the results of the animal studies mentioned above, it appears that DA may play a role in this process. D2 and D3 receptor availability is shown to be higher in the antero-ventral striatum, a brain area involved in reward, of individuals who have recovered from anorexia nervosa (Frank et al., 2005). This was found in a study in which there was no significant difference between the mean body mass index (BMI) of the participants who had recovered from anorexia nervosa and normal controls, suggesting the potentially enduring effects of food deprivation even following weight restoration.

3. Effects of overeating on reward sensitivity

3.1. Laboratory animal studies

There appears to be a strong causal relationship between food restriction and drug use, as food deprivation has been shown to increase self-administration of a number of different drugs in animals (Carr, 2002). Interestingly, overeating (with or without food restriction) may also precipitate addictive behavior, and there have been several studies that suggest neurochemical and behavioral similarities between drug addiction and the more recently researched topic of "food addiction" (Allen et al., 2012; Avena et al., 2008a; Gold et al., 2009), although there is some controversy regarding how this construct should be applied to obesity (Ziauddeen et al., 2012).

Nonetheless, there are several reports that support the idea that overeating affects brain reward systems. Behavioral evidence of decreased reward sensitivity due to overeating comes in part from findings reported by Shin et al. (2011) that show that both diet-induced obese and obesity-prone rats without access to a high-fat diet appear to prefer higher concentrations of sucrose and corn oil, while they do not show much interest in lower concentrations, indicating a higher level of tolerance toward the rewarding effects of these foods. Interestingly, this effect disappeared after a period of chronic food restriction and concomitant weight loss, supporting the idea that chronic food deprivation increases reward sensitivity. These authors have also reported that obesity-prone rats exhibit slower responding for a food reward (measured by completion speed in an incentive runway) compared to obesity resistant rats both before and after access to a high-fat diet. Notably, the obesity-prone rats exhibited significantly slower responding in the incentive runway after the period of access to a high-fat diet than before (Shin et al., 2011). Body weight gain in rats given prolonged access to a cafeteria-style diet coincided with an increase in brain stimulation reward thresholds, further indicating a heightened tolerance to the effects of reward (Johnson and Kenny, 2010).

Rats that become overweight due to access to a cafeteria-style diet show markedly greater levels of extracellular DA when administered systemic amphetamine compared to controls (Pothos, 2001), which might suggest increased, rather than decreased, reward sensitivity. However, these findings of increased DA release must be considered within the context of the effects of overeating on DA receptors. A recent study by Marco et al. (2012) revealed that OLETF rats (which have the satiety-associated cholecystokinin receptor type 1 naturally knocked out) prefer higher concentrations of a sucrose solution, whereas controls showed a decreased interest in a high (1 M) concentration of sucrose over time. Interestingly, D2 receptors in the NAc of the obese OLETF rats decreased over time compared to controls. Like the findings above, subsequent deprivation of food and concomitant weight loss resulted in an increase in D2 receptors in these rats (Marco et al., 2012). Similarly, decreased striatal D2 receptor expression has been found among dietary-induced obese rats compared to controls. Further, it appears that both overconsumption of palatable food and the knockdown of D2 receptors are associated with increased reward thresholds (Johnson and Kenny, 2010), suggesting a higher level of tolerance for reward. Additional evidence linking D2 receptor reduction to food reward comes from the finding

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