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EPISODIC SUCROSE INTAKE DURING FOOD RESTRICTION INCREASES SYNAPTIC ABUNDANCE OF AMPA RECEPTORS IN NUCLEUS ACCUMBENS AND AUGMENTS INTAKE OF SUCROSE FOLLOWING RESTORATION OF *AD LIBITUM* FEEDING

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Abstract—Weight-loss dieting often leads to loss of control, rebound weight gain, and is a risk factor for binge pathology. Based on findings that food restriction (FR) upregulates sucrose-induced trafficking of glutamatergic AMPA receptors to the nucleus accumbens (NAc) postsynaptic density (PSD), this study was an initial test of the hypothesis that episodic ''breakthrough'' intake of forbidden food during dieting interacts with upregulated mechanisms of synaptic plasticity to increase reward-driven feeding. *Ad libitum* (AL) fed and FR subjects consumed a limited amount of 10% sucrose, or had access to water, every other day for 10 occasions. Beginning three weeks after return of FR rats to AL feeding, when 24-h chow intake and rate of body weight gain had normalized, subjects with a history of sucrose intake during FR consumed more sucrose during a four week intermittent access protocol than the two AL groups and the group that had access to water during FR. In an experiment that substituted noncontingent administration of D-amphetamine for sucrose, FR subjects displayed an enhanced locomotor response during active FR but a blunted response, relative to AL subjects, during recovery from FR. This result suggests that the enduring increase in sucrose consumption is unlikely to be explained by residual enhancing effects of FR on dopamine signaling. In a biochemical experiment which paralleled the sucrose behavioral experiment, rats with a history of sucrose intake during FR displayed increased abundance of pSer845-GluA1, GluA2, and GluA3 in the NAc PSD relative to rats with a history of FR without sucrose access and rats that had been AL throughout, whether they had a history of episodic sucrose intake or not. A history of FR, with or without a history of sucrose intake, was associated with increased abundance of GluA1. A terminal 15-min bout of sucrose intake produced a further increase in pSer845-GluA1 and GluA2 in subjects with a history of sucrose intake during FR. Generally, neither a history of sucrose intake nor a terminal bout of sucrose intake affected AMPA receptor abundance in the NAc PSD of AL subjects. Together, these results are consistent with the hypothesis, but the functional contribution of increased synaptic incorporation of AMPA receptors remains to be established.

Key words: sucrose, nucleus accumbens, food restriction, AMPA receptors, postsynaptic density.

INTRODUCTION

Weight-loss dieting often leads to loss of control, poor food choices, and the regain or surpassing of baseline body weight (Rogers and Hill, 1989; Vitousek et al., 2004a,b; Polivy and Herman, 2006; Polivy et al., 2008). In fact, a history of weight-loss dieting predicts future weight gain (e.g., Lowe et al., 2006) and may contribute to obesity (Polivy and Herman, 2006). In addition, dieting periods are common in the history of binge eaters (Stice et al., 2008), and cycling between food restriction (FR) and free feeding is a strong predictor of overeating palatable food in response to stress (Wardle et al., 2000).

Previously, it was demonstrated that FR induces neuroadaptations that increase intracellular signaling and gene expression downstream of D1 dopamine (DA) receptor stimulation in nucleus accumbens (NAc; Carr et al., 2003, 2010; Haberny et al., 2004; Haberny and Carr, 2005). Among the behavioral concomitants are increased rewarding effects of D1 receptor agonists and psychostimulant drugs, and resistance to extinction of a cocaine-conditioned place preference acquired during a prior *ad libitum*-fed (AL) state (Cabeza de Vaca and Carr, 1998; Zheng et al., 2013). In light of evidence that drug addiction represents a ''hijacking'' of the neurocircuitry that mediates appetitively motivated behavior (Kelley and Berridge, 2002; Cardinal and Everitt, 2004; Di Chiara, 2005; Volkow et al., 2008; Davis and Carter, 2009; Frascella et al., 2010), the enhanced responsiveness to drugs and associated cues during FR likely reflect

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Abbreviations: AL, *ad libitum*; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANOVA, analysis of variance; DA, dopamine; FR, food restriction; MSNs, medium spiny neurons; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; PBS, phosphate-buffered saline; PMSF, phenylmethanesulfonyl fluoride; PSD, postsynaptic density.

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exploitation of neuroadaptations that normally promote foraging, reward-related learning, and ingestive behavior during periods of food scarcity. Recent developments in Western societies, including prevalent dieting and an abundance of supranormally rewarding energy-dense food, present a set of conditions with potential to ingrain another type of maladaptive behavior, namely, excessive reward-driven feeding. Evidence in support of a lasting alteration of CNS responsiveness to palatable food among historical dieters was recently provided by a functional magnetic resonance imaging (fMRI) study demonstrating that, in the fed state, historical dieters show increased activation of reward-related brain regions in response to highly palatable food when compared to nondieters and current dieters (Ely et al., 2013).

The mesoaccumbens DA pathway is involved in normal and abnormal eating behavior (Bassareo and Di Chiara, 1999a,b; Palmiter, 2007; Kenny, 2011), and mediates the reinforcing effects of most drugs of abuse (Wise and Bozarth, 1985; Pontieri et al., 1995; Feltenstein and See, 2008). Addiction research indicates that enduring changes in NAc neuronal circuitry, resulting from repeated strong activation of convergent DA- and glutamate-coded inputs, plays an important role in drug craving and compulsive use (Hyman et al., 2006). Electrophysiological studies support a view of NAc organization in which distinct neuronal ensembles encode behavior associated with different rewards, with reward type-selectivity and number of dedicated neurons subject to change as a result of experience (Pennartz et al., 1994; Carelli and Ijames, 2001; Peoples and Cavanaugh, 2003; Deadwyler et al., 2004; Cameron and Carelli, 2012). A common molecular mechanism of activity-dependent synaptic plasticity in the CNS involves trafficking of GluA1-containing AMPA receptors (Hollmann and Heinemann, 1994; Malinow, 2003; Kessels and Malinow, 2009). AMPARs are co-expressed with DA receptors in striatal neurons (Bernard et al., 1997; Glass et al., 2008), and most NAc AMPARs are either GluA1/GluA2 or GluA2/GluA3 heteromers (Reimers et al., 2011). GluA2/GluA3 traffic constitutively to synapses, while trafficking of GluA1-containing receptors is dependent on synaptic activity (Barry and Ziff, 2002; Greger et al., 2007). AMPAR trafficking in NAc has been implicated in sensitization, craving, and relapse to cocaine seeking (Cornish et al., 1999; Cornish and Kalivas, 2000; Boudreau and Wolf, 2005; Conrad et al., 2008; Famous et al., 2008; Wolf and Ferrario, 2010, pp. 65–72; Xie et al., 2011), and Ca^{2+}-permeable AMPARs in NAc have been implicated in the enhanced rewarding effects of amphetamine and D1 receptor stimulation in FR rats (Carr et al., 2010; Peng et al., 2014).

Phosphorylation of GluA1 on Ser845 by the D1 receptor-regulated cAMP pathway (Roche et al., 1996; Greger et al., 2007; Esteban et al., 2003; Boehm et al., 2006; Oh et al., 2006; Ehlers et al., 2007; Man et al., 2007; He et al., 2009; Lee, 2012), or the N-methyl-D-aspartate (NMDA) receptor-regulated cGKII pathway (Serulle et al., 2007) increases neuronal excitability and serves as the first of two steps whereby cytoplasmic AMPARs are trafficked to the synapse as the mechanistic underpinning of experience-dependent behavioral plasticity (Shi et al., 2001; Barry and Ziff, 2002; Derkach et al., 2007; Kessels and Malinow, 2009). Activation of this mechanism in D1 DA receptor-expressing NAc medium spiny neurons (MSNs) would be expected to increase reward-directed behavior (Lobo et al., 2010; Lobo and Nestler, 2011). It is therefore of interest that a brief intake of 10% sucrose was shown to increase NAc phosphorylation of GluA1 on Ser845 in FR but not AL rats (Carr et al., 2010). Further, seven consecutive daily 5-min episodes of sucrose intake increased GluA1 abundance in the NAc postsynaptic density (PSD), and quantitative electron microscopy revealed an increased intraspinous GluA1 population (Tukey et al., 2013). Comparing AL and FR rats, it was found that sucrose intake increased GluA1 and GluA2 abundance in the PSD with a greater effect in FR rats (Peng et al., 2011). Given the role of AMPARs in synaptic strengthening (Malinow, 2003; Whitlock et al., 2006; Greger et al., 2007) and behavior modification (Whitlock et al., 2006; Kessels and Malinow, 2009), the FR-induced upregulation of sucrose-induced AMPAR trafficking may cause episodes of loss of control during severe dieting to increase vulnerability to excessive sucrose consumption after free-feeding conditions have resumed.

To test predictions of this hypothesis, subjects in the present study had episodic limited access to sucrose or tap water during FR or AL diet conditions. FR subjects were then returned to AL feeding and experimental testing was initiated only after daily chow intake had normalized. Testing consisted either of measuring 1-h intake of 10% sucrose three times per week for four weeks, or obtaining NAc tissue samples for biochemical assay following 15-min access to sucrose or water, or removal of subjects from the home cage without fluid access. Two predictions were tested: (1) Rats with a history of episodic sucrose intake during FR would consume more sucrose than both (i) rats with an identical history of FR but without sucrose intake, and (ii) rats with an identical history of sucrose intake but without FR; (2) Rats with a history of episodic sucrose intake during FR would display increased AMPAR abundance in the NAc PSD relative to both (i) rats with an identical history of FR but without sucrose, and (ii) rats with an identical history of sucrose intake but without FR.

EXPERIMENTAL PROCEDURES

Experimental procedures were approved by the Institutional Animal Care and Use Committee at the New York University School of Medicine and were consistent with the *Principles of Laboratory Animal Care* (NIH Publication No. 85–23).

Experiment 1

Subjects and feeding regimens. Subjects were 40 mature, male Sprague–Dawley rats (Taconic Farms, Germantown, NY, USA) weighing between 350 and 450 g at the start of the experiment. They were