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Neuropsychopharmacology Reviews (2017) **42**, 360–361; doi:10.1038/npp.2016.228

Food Addiction and Obesity

The obesity epidemic in the US and abroad has increased interest in neurobiological mechanisms that contribute to eating in the absence of energy demand or hunger (overeating). Overeating, sometimes called ‘hedonic’ feeding because foods consumed are usually palatable and high in sugars and fats, is the leading cause of overweight and obesity in the US. One important factor that contributes to obesity is overeating triggered by sights, sounds, and smells (food cues) associated with palatable food (Stice *et al*, 2013; Tang *et al*, 2012). For example, obese and overweight people report greater food craving and consume larger portions in response to food cues. A wealth of preclinical studies have demonstrated that these cue-triggered motivational responses are mediated by brain mesocorticolimbic circuits, particularly dopamine and glutamate transmission within the nucleus accumbens (NAc). In humans, the magnitude of activations in the NAc in response to food cues predicts future weight gain in normal-weight people and inability to lose weight after obesity onset. This suggests that differences in NAc function may mediate enhanced cue-triggered urges to eat in susceptible individuals both

before and after weight gain. The overlap in the neural systems involved and similarities between responses to food, addictive drugs, and cues associated with them have sparked vibrant discussion about ‘food addiction’ (Carter *et al*, 2016), despite some obvious differences between food and drug (eg, food does not have psychoactive properties in the pharmacological sense, nor is there a clear dose-response relationship, etc.). So, can overeating that produces common obesity really be considered a form of addiction?

In a recent preclinical study we found that, prior to any diet manipulation, those rats that show the strongest motivational responses to a food cue subsequently gained the most weight when given free access to a fatty, sugary, ‘junk-food’ diet (Robinson *et al*, 2015). Obesity-prone rats are also more sensitive to the locomotor-activating effects of cocaine, indicating enhanced responsivity of mesolimbic systems, and have greater excitability of medium spiny neurons in the NAc core prior to the development of obesity (Oginsky *et al*, 2016a, b). Taken together, our data suggest that pre-existing enhancements in NAc responsivity may render obesity-susceptible individuals more sensitive to the motivational properties of food cues. In addition, consumption of fatty, sugary foods alters NAc function in ways that also vary by susceptibility to obesity. For example, consumption of junk food enhances NAc glutamatergic transmission and produces an upregulation of calcium-permeable AMPA receptors (CP-AMPA) in obesity-susceptible rats (Brown *et al*, 2015; Oginsky *et al*, 2016a). Interestingly, increases in CP-AMPA were found prior to obesity onset, suggesting that they may drive enhanced motivational responses that promote weight gain (see Oginsky *et al*, 2016b for further discussion).

Enhanced cue triggered motivation and accompanying increases in NAc responsivity are thought to underlie drug addiction (Flagel *et al*, 2009), and NAc CP-AMPA mediate enhanced cue-triggered cocaine-seeking (Wolf, 2016). One pressing question

that arises, however, is the extent to which the enhanced neurobehavioral responsivity found in obesity-susceptible rats is a form of *aberrant* motivation, akin to drug addiction. Brain reward circuits evolved in part to direct behavior towards food. Thus, enhancements in NAc responsivity and cue-triggered motivation could be described as an improved function of this system (ie, rendering individuals better able to find food) rather than dysfunction. Of course, not being able to curb cue-triggered urges in the current calorie-dense food environment is unhealthy, and it is not entirely clear where this idea leaves obesity-resistant individuals. Are they the outliers? However, to develop better prevention strategies for obesity it will be important to differentiate ‘normal’ neurobehavioral responses from fundamentally aberrant ones and to continue to challenge ourselves by asking these questions.

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The Emerging Role of Innate Immunity in Alzheimer's Disease

The amyloid cascade hypothesis is the dominant model for Alzheimer's disease (AD) pathology and has guided AD drug development strategies for over two decades. The hypothesis states that excessive cerebral accumulation of β -amyloid plaques from oligomerization of amyloid- β protein ($A\beta$) drives a neurodegenerative cascade, including generation of neurofibrillary tangles (NFTs) from tau protein. NFTs are a hallmark pathology for AD. Overwhelming genetic and biochemical data support the primacy of $A\beta$ fibrillization pathways in AD pathology. A landmark study by Choi *et al* (2014) also recently confirmed that β -amyloid generation leads to NFTs in novel 3D human neuronal cell culture models that recapitulate AD pathologies (Choi *et al*, 2014). However, the roles played by $A\beta$ and β -amyloid in the amyloid cascade model has shifted markedly during the last two decades. Initially, insoluble β -amyloid plaques were viewed as driving neurodegeneration. The key species mediating AD pathology are now thought to be soluble oligomeric intermediates generated during $A\beta$ fibrillization. The near future may see

Figure 1. $A\beta$ oligomer pathways and potential targets for therapeutic intervention. Recent studies of 'resilient' brains with high senile plaque loads have shown β -amyloid alone is insufficient for AD neurodegeneration. Neurofibrillary Tangles (NFTs) and neuroinflammation are also required. Shown are oligomer-mediated pathways contributing to neurodegeneration in AD and potential points for intervention (X). Possible approaches emerging from the antimicrobial peptide role of $A\beta$ are indicated (??) as well as established therapeutic strategies, including secretase modulators that reduce the 42 amino acid $A\beta$ isoforms (eg, GSM, NS-GSI, BSI), copper chelators (eg, PBT2), $A\beta$ oligomerization blockers (eg, PBT2, ELND005, NRM8499), immunotherapies aimed at antibody-mediated clearance of $A\beta$ (eg, Bapi, Sola), antioxidants that attenuate ROS-mediated inflammation (eg, vitamin E, epigallo-catechine gallate, resveratrol), agents purported to be neuroprotective (eg, dimebon), and drugs that inhibit tau aggregation and NTF generation (eg, rhodanine-based and Phenylthiazolyl-hydrazide inhibitors).

further substantial adjustments to the amyloid cascade model if recent findings of an antimicrobial function for $A\beta$, and links between AD and innate immune genes (Bertram and Tanzi, 2012) are confirmed. Importantly, new innate immune models of AD amyloidosis are likely to be of considerable interest for ongoing and future AD therapeutic efforts (Figure 1).

In prevailing models of AD amyloidogenesis, $A\beta$'s propensity to oligomerize and generate β -amyloid is viewed as an intrinsically abnormal and exclusively pathological activity. However, recent findings suggest $A\beta$ oligomerization may help protect the brain from infection. $A\beta$ shows potent *in vitro* microbicidal activities against human pathogens, consistent with identity as an antimicrobial peptide (Soscia *et al*, 2010). $A\beta$ expression also

significantly increases survival of transgenic mice in acute encephalitis models (Kumar *et al*, 2016). Moreover, fibrillization appears to mediate the protective activities of $A\beta$ in brain and leads to the concentration and entrapment of pathogens within β -amyloid deposits (Kumar *et al*, 2016). Confirmation of a physiological role for β -amyloid generation would shift the modality of $A\beta$'s pathophysiology from abnormal stochastic behavior toward dysregulated innate immune response. This suggests a response to perceived immunochallenge may mediate AD amyloidosis. This may involve sterile inflammatory stimuli, as with aseptic inflammation diseases. Or alternatively, AD amyloidosis may be driven by subclinical chronic cerebral infection. It remains unclear if infection precedes the establishment of the amyloid cascade in AD brain.