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A COMMON GENETIC ETIOLOGY FOR IMPULSIVITY AND OVEREATING

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ABSTRACT

In its most basic form impulsivity, a heritable trait, is defined as a tendency to act without control and has been implicated in the onset, symptomatic expression, and maintenance of overeating. Specifically, high impulsivity and its related constructs such as poor inhibitory control and high sensitivity for reward and environmental cues have been shown to perpetuate binging and overeating. Thus, several studies have been conducted to investigate the possible common genetic etiologies for high impulsivity and overeating. The purpose of this review is to summarize the genetic findings indicating an association between impulsivity and overeating.

Keywords: Overeating, Impulsivity, Polymorphism, Genetic, Impulse control, Binge eating

Introduction

Impulsivity, a personality trait broadly defined as acting without thinking, is routinely associated with high- risk decision-making and behaviors, and is suggested to be a mediator modulating eating behavior towards overeating and lack of control in eating behavior. Specifically, research showed prevalence of impulsivity in patients with binge-eating disorder (BED) (Schag, Schonleber, Teufel, Zipfel, & Giel, 2013) which is a psychiatric disorder characterized by frequent episodes of binge eating and loss of control over food intake. In line with this, studies have shown impulsivity to be positively correlated with body mass index (BMI) (Meule & Blechert, 2017), difficulty in weight maintenance (Weygandt et al., 2015), and tasty but unhealthy food choices (Kakoschke, Kemps, & Tiggemann, 2015). Furthermore, in children, higher impulsivity was also shown to associate with a greater risk of becoming obese in adulthood (Fields, Sabet, & Reynolds, 2013), and with difficulty in weight loss (Nederkoorn, Jansen, Mulkens, & Jansen, 2007).

Impulsivity is a multidimensional construct with several facets, characterized primarily by disinhibited and rapid spontaneous response without consideration of possible consequences (i.e. urgency and lack of perseverance) and heightened drive towards pleasurable stimuli (i.e. reward sensitivity). Altered reward sensitivity (measured by longer cue gazing duration and difficulty in inhibiting saccades toward cues) has been shown in persons with BED (Schag et al., 2013) and a sub-group of those with bulimia nervosa (BN; another psychiatric disorder characterized by cycle of binging with compensatory self-induced vomiting) that is frequently categorized as ‘‘multi-impulsive” (Wonderlich et al., 2005). Similarly, enhanced appetite towards reward-signaling cues (i.e. food cues), termed as ‘cue-reactivity’ (Jansen et al., 2008), as well as attention and memory biases towards food cues were all observed in obese persons (Meule, de Zwaan, & Muller, 2017), and persons with binging type of eating disorders (Schmitz, Naumann, Biehl, & Svaldi, 2015). Moreover, adolescents with binge eating habits and lack of control over eating were shown to exhibit greater reward sensitivity, engage in impulsive behaviors, and possess a tendency to engage in rash behavior when distressed (Fields et al., 2013). Overall, these findings indicate a strong association between overeating and impulsivity trait that may partially implicate causality.

The search for a causal link between impulsivity and overeating has led researchers to attempt to determine a common genetic etiology. This review briefly summarizes the recent findings on the known genetic tendencies that suggest impulsivity as a heritable trait that is intermediary and shares genetic components with overeating, highlighting the need to address the impulsivity trait for more effective obesity interventions.

Dopamine-Related Genes

Dopamine (DA) is known to play a critical role in reward-related processes and the key modulator within the meso-limbo-cortical system of which the activity has been implicated in the actual reward processing and immediate reward value. It has been shown that both acute exposure to and anticipation of food intake result in DA release (Volkow & Baler, 2015). In addition, greater activity in the mesolimbic dopaminergic regions of the meso-limbo-cortical system has been reported in response to food cues in obese persons (vs. lean persons) (Stoeckel et al., 2008) and in obese persons with BED (vs. non-BED) (Geliebter et al., 2006). Moreover, impaired mesolimbic dopaminergic signaling in overeating and lower *dopamine receptor* (*D2DR*) availability in obese persons have also been shown (Wang et al., 2001).

It is known that the activity in the dopaminergic mesocortical pathway of the meso-limbo-cortical system is involved in impulsive action, behavioral inhibition, reward prediction error (cognitive flexibility and decision-making as well as mediating neural responses for sensory specific processes for taste (Volkow & Baler, 2015). Increased activity in this pathway has been shown to be negatively correlated with impulsive action (Uher & Treasure, 2005) and reduced activity in this pathway has been associated with palatable food intake (Stice, et al., 2008a) and higher body weight (Batterink, et al., 2010). Thus, the functional relevance of DA to both impulsivity trait and overeating encouraged the researchers to conduct studies to investigate the polymorphisms on the expression of the encoding DA- related genes in relation to overeating and the impulsivity trait.

It is known that the *ANKK1* (*ankyrin repeat and protein kinase domain-containing protein*) gene is involved in DA synthesis and promotes the gene for DRD2 (Neville, Johnstone, & Walton, 2004). The *TaqIA* polymorphism on *ANKK1* gene, specifically on the *A1* allele (*TaqIA* $A1^+$) causes low DA synthesis and is associated with diminished (30-40%) *DRD2* density, overall leading to reduced DA function (Jonsson et al., 1999). The *TaqIA* $A1^+$ polymorphism was shown in patients with BED (Davis et al., 2012), and has been associated with overeating, prospective weight gain (Stice, Spoor, Bohon, & Small, 2008b), and higher BMI as well as stronger response to food reinforcement in

obese persons (Epstein et al., 2007). It was shown to predict the weight loss outcomes in children (Chan et al., 2014) and the neural activity in response to ingestion of palatable foods, independent of BMI (Felsted, et al., 2010). *TaqIA A1*$^{+}$ polymorphism was also shown to associate with impulsivity and reward seeking (Chen et al., 2007*).*

A functional polymorphism which produces a valine (val)/methionine (met) substitution at *codon 158 (val158met variant)* on the gene encoding the catechol-*O*-methyl transferase (*COMT*) -an enzyme responsible for the DA catabolism in the meso-limbo-cortical system, causes greater enzymatic activity, which results in higher DA degradation and catabolism and thus low DA levels (Bilder, Volavka, Lachman & Grace, 2004). The *Val*^{158}*Met* polymorphisms have been associated with total adiposity (i.e. abdominal), fat intake, unhealthy food choices and overall desirability to food as well as susceptibility for BED (Leehr et al., 2016; Wallace et al., 2015). It is also associated with impulsive action decreased function in the prefrontal cortex, a region of the brain for executive function and decision making, and greater responsivity to reward in a reward seeking/risk taking task (Bilder et al., 2004; Lancaster, et al.,2012).

An interaction effect has been reported between *DAT1* gene mutation, causing lower DA transmission and *COMT* polymorphism on cognitive flexibility and reward-related neural activity (Yacubian et al., 2007) as well as maladaptive eating patterns including binging (Hersrud & Stoltenberg, 2009). Another study showing effect of the *DAT1* genotype independent of *COMT* genotype (Aarts et al., 2010), however, in this study, the group sizes did not allow the authors to do analyze separately, instead they have used *COMT* genotype as a covariate in their analysis. A similar interaction effect has been reported between *COMT (Val158Met)* and dopamine *D4 receptor (DRD4)* on low cognitive inhibition and binging (Heinzel et al., 2012). The exon-3 seven-tandem repeats (*7R*) allele of the *DRD4* gene is known to cause low DA activity, possibly via decreased receptor expression and maturation, which then leads to significantly higher amounts of DA being required to induce the same response produced by the other alleles (Asghari et al., 1995). The *DRD4 7R allele* has been associated with insufficient prefrontal cortex function for response control leading vulnerabilities for impulsivity and impulsivity-related psychiatric conditions as well as binge eating and concomitant weight gain (Steiger et al., 2016).

Collectively, these studies indicate that genetic disruptions in the mesolimbic DA signaling cause impairments in reward processing, thus cause sensory deprivation of the brain's reward or pleasure mechanisms, and purport the individual's biochemical ability to derive reward from a threshold of what people normally achieve. This eventually may lead to behavioral compensation of reward-seeking and thus promote overeating. Moreover, impaired behavioral control, perhaps arising from genetic disruptions in mesocortical DA activity, may be promoting overeating by inhibiting the individual's ability to suppress food intake through diminished behavioral impulse control.

Serotonin-Related Genes

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is well known to affect mood, personality, and eating behavior. Mutations of the genes encoding for 5-HTP transporter and 5-HTP *receptor (HTR2A and HTR2B)* have been implicated in the impulsivity trait and overeating (Bevilacqua & Goldman, 2013; Kuikka et al., 2001). Decreased 5-HT activity has been associated with binging behavior in eating disorders. Specifically, downregulation of 5-HT transporters was found in obese women with BED (Kuikka et al., 2001), and upon recovery the 5-HT transporter was reported to be upregulated (Tammela et al., 2003). This suggests that the effect of 5-HT is transient and may be a consequence of psychopathology. Consistent with these, obesity was shown to associate with polymorphisms on the genes encoding for 5-HT transporter (Zhao, et al., 2013) and 5-HT2A receptors (Erritzoe et al., 2009), causing decreased 5-HT levels. Decreased 5-HT activity has also been associated with the impulsivity trait (Stoltenberg, Christ, & Highland, 2012). Together these may suggest that polymorphisms leading to low 5-HT activity may be specific to lack of control over eating episodes in persons with high impulsivity. Although an association between the dysregulation in the 5-HT system and overeating has been reported, the direction of the effect and a possible mediator effect of the impulsivity trait as an endophenotype for overeating has yet to be determined by further studies.

***FTO* Gene**

Variants in the *FTO (*fat mass and obesity associated) gene were the first single nucleotide polymorphisms robustly associated with high BMI. It is known to be the best candidate to predict genetic obesity (Chuang et al., 2015) and to regulate dopaminergic activity (Hess et al., 2013). Recent studies have shown that, similar to dopamine, the *FTO* gene displays a differential role in food intake perhaps through altered reward processing as well as diminished impulse control. The carriers of the certain variants in the *FTO* gene were also shown to predict larger volumes of nucleus accumbens, a reward-related brain area, (Rapuano et al.,

2017), reduced prefrontal cortex function during aging (Chuang et al., 2015), reduced frontal lobe volume (Ho et al. 2010). It is possible that the *FTO* gene to be involved in the modulation of the prefrontal cortex responses leading to greater impulsivity and reward seeking. This may partially contribute to the mechanism underlying the possible causal effect *FTO* genotype on obesity.

Opioid Receptor Gene

The *G allele (G+)* of the *A118G* polymorphism of the μ-opioid 1 receptor encoding gene (*OPRM1*) has been found to be prevalent in obese persons with BED (vs. obese non-BED persons) (Davis et al., 2009).

Studies have suggested abnormal opioid transmission in prefrontal cortex and nucleus accumbens may lead to deficits in impulse control (Selleck et al., 2015) and altered acitivity in these areas have also been shown to be related to problems in impulse control in overeating and binge eating (Dong et al., 2016). Thus, individuals may be prone to elevated food-related hedonic responses through dopaminergic and opioidergic influences on reward-related processes.

Neuregulin 3 Gene

Recent preclinical data has shown that expression for *neuregulin 3 (Nrg3)* genes in the amygdala -a key region for fear and emotion processing, and in the prefrontal cortex may be involved in the development of the impulsivity trait (Pietrzykowski & Spijker, 2014). The amygdala and its efferent projections to mesolimbic pathway have been implicated in incentive learning and reward value processing (Blaiss & Janak, 2009). Recent findings show that the amygdala is also playing a role in addiction as well as impulsive choice and actions (Depue et al., 2014). The basolateral nucleus of amygdala encodes emotional events with reference to their particular sensory-specific features and motivational or affective significance, and it has been known to receive afferents from visceral brainstem and hypothalamus and to send projections to dopaminergic meso-cortico-limbic structures. Although it is premature to assume that an effect of the *Nrg3* gene expression causes a link between impulsivity and overeating in humans, it is a novel candidate gene requiring further attention.

Conclusion

In light of these findings, although the underlying mechanisms remain unknown, a causal link between impulsivity trait and overeating seems possible. The interplay between the genetic and neurobiological impulsivity markers, and the neuropeptides and gut hormones could be addressed in future studies with the goal of tracking common genetic factors and their contributions to the neurobiological bases. Elucidation of possible mediation of the eating behavior by the impulsivity trait may allow us better understand the resistance to lifestyle interventions.

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