Pharmacology and Therapeutics 182 (2018) 15–27

Contents lists available at ScienceDirect

Pharmacology and Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: F. Tarazi

Binge-eating disorder: Clinical and therapeutic advances

Peter H. Hutson[a,*], Iris M. Balodis[b], Marc N. Potenza[c,d,e,f]

[a] Department of Neurobiology, CNS Discovery, Teva Pharmaceuticals, West Chester, PA, USA
[b] Peter Boris Centre for Addiction Research, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
[c] Department of Psychiatry, Child Study Center, Yale University School of Medicine, New Haven, CT, USA
[d] Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA
[e] National Center on Addiction and Substance Abuse, USA
[f] Connecticut Mental Health Center, New Haven, CT, USA

ARTICLE INFO

Keywords:
Binge-eating disorder
Impulsivity
Compulsivity
Reward
Neurobiology
Pharmacotherapy

ABSTRACT

Binge-eating disorder (BED) is the most prevalent eating disorder with estimates of 2–5% of the general adult population. Nonetheless, its pathophysiology is poorly understood. Furthermore, there exist few therapeutic options for its effective treatment. Here we review the current state of binge-eating neurobiology and pharmacology, drawing from clinical therapeutic, neuroimaging, cognitive, human genetic and animal model studies. These studies, which are still in their infancy, indicate that while there are many gaps in our knowledge, several key neural substrates appear to underpin binge-eating and may be conserved between human and animals. This observation suggests that behavioral intermediate phenotypes or endophenotypes relevant to BED may be modeled in animals, facilitating the identification and testing of novel pharmacological targets. The development of novel, safe and effective pharmacological therapies for the treatment of BED will enhance the ability of clinicians to provide optimal care for people with BED.

1. Introduction

Binge-eating disorder (BED) is the most prevalent eating disorder occurring in 2–5% of the adult population and is more common in females than males (Dingemans, Bruna, & van Furth, 2002; Kessler et al., 2013). BED is characterized by compulsive episodes of excessive consumption of highly palatable foods (binges) together with a strong sense of loss of control. Binge-eating episodes are often accompanied by feelings of anxiety, shame, disgust and guilt but unlike other eating disorders there is an absence of compensatory purging behaviors. BED is often associated with obesity although a significant proportion of subjects (17–30%) have normal body weights (Fairburn, Cooper, Doll, Norman, & O'Connor, 2000; Goldschmidt et al., 2011). Until recently (McElroy, Hudson, et al., 2016; McElroy, Mitchell, et al., 2016), there were no approved pharmacological treatments for BED and clinicians relied upon cognitive behavioral therapy often in combination with the off-label use of pharmacotherapies such as selective serotonin reuptake inhibitors, anti-obesity agents or anticonvulsants Grilo, Reas, & Mitchell, 2016; Palavras, Hay, Filho, & Claudino, 2017). Here we review the current state of knowledge of the neurobiology and neuropharmacology of BED from a clinical and basic science perspective including the development of animal models which target relevant behavioral intermediate phenotypes or endophenotypes that are at the core of BED. Based on these clinical observations and animal model data, we also highlight some of the advances being made in the identification and validation of novel pharmacotherapies for the treatment of BED.

2. Neurobiology of binge-eating behavior

The neurobiology of BED is relatively poorly understood but is gradually evolving and has been recently reviewed (Balodis,

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; BED, Binge-eating disorder; BOLD, Blood-oxygen-level dependent; BMI, Body mass index; BN, Bulimia nervosa; CNS, Central nervous system; DSM 5, Diagnostic and statistical manual of mental disorders, fifth edition; IFG, Inferior frontal gyrus; PET, Positron emission tomography; SPECT, Single photon emission computerized tomography; 5-HT, Serotonin; rCBF, Regional cerebral blood flow; PFC, Prefrontal cortex; fMRI, Functional magnetic resonance imaging; OFC, Orbitofrontal cortex; PCC, Posterior cingulate cortex; MIDT, Monetary incentive delay task; tDCS, Transcranial direct current stimulation; dlPFC, Dorsolateral prefrontal cortex; GMV, Gray matter volume; LDX, Lisdexamfetamine; SSRI, Selective serotonin reuptake inhibitor; YBOCS-BE, Yale-Brown obsessive compulsive scale modified for binge-eating; FDA, U. S. Food and Drug Administration; TAAR, Trace amine receptor; GABA, Gamma amino butyric acid; OX1 and OX2, Orexin receptor subtypes; NOP, ORL1/nociceptin-opioid-peptide; NMDA, *N*-methyl-D-aspartate; CB1 and CB2, Cannabinoid receptor subtypes; 2-AG, 2-Arachidonoylglycerol; FAAH, Fatty acid amide hydrolase; MAGL, Monoacylglycerol lipase; PPARs, Peroxisome proliferator activated receptors; TRPV, Transient receptor potential ion channels; PG, Pathological gambling

* Corresponding author at: Neurobiology, CNS Discovery, Teva Pharmaceuticals, West Chester, PA 19380, USA.
E-mail address: peter.hutson@tevapharm.com (P.H. Hutson).

http://dx.doi.org/10.1016/j.pharmthera.2017.08.002

Available online 19 August 2017

Grilo, & Potenza, 2015; Kessler, Hutson, Herman, & Potenza, 2016). There is a growing consensus derived from clinical functional imaging and cognitive studies that several interconnected behavioral intermediate phenotypes including attentional bias towards food cues, cognitive flexibility, perseverative or compulsive behavior, impulsivity (Voon, 2015), motivation and reward processing are impaired in BED (Balodis & Potenza, 2015; Manwaring, Green, Myerson, Strube, & Wilfley, 2011). These clinical observations are supported by pharmacological and behavioral studies of the fundamental processes underpinning natural and drug rewards, impulsivity, compulsivity and habitual behavior including the potential role of the mesolimbic dopamine system where the phasic release of dopamine in the ventral striatum motivates animals to seek food. Intriguingly this key pathway is influenced by peripherally originating orexigenic peptides (*e.g.*, ghrelin) acting on specific receptors located in brain stem dopamine and cholinergic cell bodies that modulate ascending dopamine projections to the nucleus accumbens (Liu & Borgland, 2015; Valdivia, Cornejo, Reynaldo, De Francesco, & Perello, 2015). This pathway provides not only a potential integrative mechanism between appetite, food intake and motivated behavior but also a novel target for the attenuation of behaviors linked to food or drug rewards. Additionally, animal studies have identified the involvement of several neurotransmitter signaling pathways in models of binge-eating. However, there is a paucity of positron emission tomography (PET) or single photon emission computerized tomography (SPECT) imaging studies that can affirm the involvement of these neurotransmitter pathways in BED subjects (reviewed Kessler et al., 2016). Functional genetic polymorphisms have been associated with BED (Bevilacqua & Goldman, 2013; Davis et al., 2009; Hess et al., 2013), and as with other psychiatric disorders, it is likely that no single gene is responsible and that multiple genes interacting with environmental factors (Cyders & Smith, 2008; Danner, Evers, Sternheim, & Meer, 2013; Klatzkin, Gaffney, Cyrus, Bigus, & Brownley, 2016; Vucetic, Carlin, Totoki, & Reyes, 2012) are likely to contribute to the potential of developing BED. Replication and expansion of these genetic, behavioral, neuroimaging and pharmacological studies will be invaluable in our further understanding of the neurobiology of BED.

2.1. Single photon emission computed tomography (SPECT) studies

The first neuroimaging study in individuals with BED occurred almost 2 decades ago and applied [99mTc]ethyl-cysteine-dimer with SPECT to examine neural responses to neutral versus food cues (Karhunen et al., 2000). Participants consisted of obese BED females recruited from weight-loss programs as well as obese non-BED and lean control females. Following an overnight fast, participants were exposed to a neutral landscape picture or to a self-selected full meal. In BED participants, blood flow was markedly increased to frontal and prefrontal regions relative to the other two groups. Although BED and non-BED groups did not differ on eating desire or food pleasantness, only the BED group showed a positive correlation between hunger and regional cerebral blood flow (rCBF) in the left prefrontal cortex (PFC). Peripheral physiological responses were measured through serum insulin, plasma glucose, serum leptin, noradrenaline, adrenaline and cortisol at multiple time points; however, no group differences were observed (Karhunen et al., 2000).

Another SPECT study by this research group examined serotonin (5-HT) binding in obese females in a scan before as well as after successful treatment (Tammela et al., 2003). Results showed that relative to control subjects, symptomatically recovered BED individuals showed significant increases in 5-HT binding in the midbrain, relative to control subjects whose binding remained unchanged between the two scans. The therapy consisted of group psychotherapy as well as fluoxetine — thereby making it difficult to disentangle each therapeutic intervention. Nonetheless this first neuroimaging treatment outcome study in BED demonstrated enhanced serotonergic binding following treatment.

2.2. Functional magnetic resonance imaging (fMRI) studies

Since the first SPECT studies, several functional magnetic resonance imaging (fMRI) studies have assessed relevant cognitive constructs in BED, including food-reward processing, non-food reward processing (*e.g.* money) as well as inhibitory control. These studies further support the notion of amplified food-cue sensitivity in BED, particularly through increased BOLD responses in reward and attention networks. Recently, fMRI investigations are moving beyond activation studies and are examining connectivity between regions as well as using computational modeling of choice behaviors. Most recently, studies are linking imaging with treatment outcome and using brain stimulation techniques in the hopes of better identifying therapeutic targets.

2.2.1. Food reward processing

Exposure to appetizing food cues increases activity in the insula and the orbitofrontal cortex (OFC) across multiple groups, including obese and non-obese populations as well as individuals with bulimia nervosa (BN) (Porubská, Veit, Preissl, Fritsche, & Birbaumer, 2006; Schienle, Schafer, Hermann, & Vaitl, 2009; Wang et al., 2011), perhaps not surprisingly as these brain regions comprise primary and secondary taste cortices, respectively (Baylis, Rolls, & Baylis, 1995; Rolls, Yaxley, & Sienkiewicz, 1990). However, BED individuals in particular demonstrate increased prefrontal activity relative to other disordered eating groups and healthy control subjects when viewing palatable food cues (Geliebter et al., 2006; Schienle et al., 2009; Simon et al., 2016). Specifically, the OFC appears as a critical area distinguishing food-cue reactivity in BED, relative to obese non-BED, lean control and BN groups, with activity here positively correlating with reward sensitivity (Schienle et al., 2009) and trait food craving (Simon et al., 2016). The role of the OFC in BED is particularly relevant given its role in taste (Baylis et al., 1995; Rolls et al., 1990); additionally, the OFC integrates sensory information to signal the subjective value of a stimulus and thereby contributes importantly to choice behavior (Kringelbach & Rolls, 2004; Levy & Glimcher, 2012). These early findings support the notion of increased sensitivity to food reward in BED. Additionally, applying a classification analysis based on neural responses as individuals view palatable foods demonstrates that activity in many of the reward processing regions, including the OFC and striatum, can be used with fair accuracy to identify individuals with BED relative to non-BED obese or BN individuals (Weygandt, Schaefer, Schienle, & Haynes, 2012).

Many studies of disordered eating distinguish between anticipatory food intake and food receipt in BED. This distinction is important as anticipatory reward processes are thought to contribute to energy intake, with heightened signaling prompting overeating (Epstein et al., 2007; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Roefs, Herman, Macleod, Smulders, & Jansen, 2005). Activity in different brain regions have been linked to anticipatory versus consummatory phases of reward, with anticipatory reward signaling recruiting ventral striatal areas, whereas consummatory, or outcome phases engaging medial PFC areas (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003; McClure, York, & Montague, 2004). A recent study probed anticipatory-consummatory phases of food reward in a combined BN and BED group of individuals with binge eating (Simon et al., 2016). The investigators reported no anticipatory striatal differences for food reward between binge-eating individuals and a non-binge-eating group (Simon et al., 2016). One brain area that did demonstrate differential signaling during anticipatory processing was the posterior cingulate cortex (PCC); the healthy control group demonstrated increased signaling here relative to the binge-eating group.

Further group differences emerged during the outcome reward phase. The binge-eating group showed greater OFC, anterior and medial PFC as well as PCC activity. These findings demonstrate phase specificity of reward sensitivity in binge-eating predominantly in the