Bulimia Revisited

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1. Introduction

The eating disorder bulimia nervosa has a prevalence in European women of about 1-2%. It also has a much higher prevalence in females compared to males, with bulimia having a sex ratio of about 10:1 (Himmerich et al., 2019; Keski-Rahkonen & Mustelin, 2016). Bulimia most often occurs during adolescence, with a mean age at onset of about 18 years old and a median age of 12.4 (Swanson et al., 2011; Volpe et al., 2016). Bulimia nervosa consists of two key features. First is a binging phase where a person will consume abnormally large amounts of food, binge eat, and often feel a loss of control. These binges can consist of any type of food but often include foods that are high in carbohydrates and fats (Hadigan et al., 1989). This is followed by compensatory behaviours which can involve purging or non-purging mechanisms due to feelings of guilt and to prevent weight gain. These include excessive exercise, laxatives or diuretics misuse, the inappropriate use of illegal or prescription drugs for weight control, fasting, and/or self-induced vomiting, with self-induced vomiting being the most common compensatory mechanism in adults (American Psychiatric Association, 2013; National Eating Disorders Collaboration; Stiles-Shields et al., 2012; Svaldi et al., 2019). Bulimic patients may also be binge eating as a means of distraction from negative emotions and then purging as a means to lower the distress caused by binging. Negative effect has been shown to decrease in patients after they purge (Turton et al., 2017). Bulimia can range from mild, when compensatory behaviours occurring 1-3 times a week to severe with an average of 8-13 compensatory behaviours a week (American Psychiatric Association, 2013). A person with bulimia can get lost in this cycle of binging and then purging as an attempt to control their shape and weight. They will also have periods of dietary restraint and restriction. They tend to experience weight fluctuations but do not lose weight, with many being in a normal weight range (Hay, 2020). This may lead to feelings of shame, guilt, and disgust with themselves and as their behaviours become more uncontrollable and compulsive it often leads to obsessive behaviours (National Eating Disorders Collaboration).

The etiology for developing bulimia is still not fully understood but there are known comorbidities and risk factors that may drive the behaviour. Traditionally it was thought that sociocultural factors may cause an idealization of a thin body and may perpetuate the dissatisfaction a person may feel about their body (Brambilla, 2001; Stice, 1994). Ballet, wrestling, gymnastics and ice skating are some examples of sports which have a heavy focus on thinness and weight restriction and they are associated with a higher incidence of bulimia (Stoutjesdyk & Jevne, 1993). People with bulimia are often described as being perfectionists, neurotic, obsessive-compulsive, harm avoidant, and uncooperative. Those with bulimia specifically have been known to have high impulsivity, sensation and novelty seeking and other traits that have been previously associated with borderline personality disorder and substance abuse (W. Kaye, 2008). There seems to be a genetic component to bulimia nervosa but the heritability ranges from about 50% to 80% when research has been done in twin studies (Bulik et al., 1998; Kendler et al., 1991). There are many psychiatric comorbidities with bulimia. These can include substance use disorder, stress disorders, personality disorders, impulse control disorders, anxiety, and depression (Brambilla, 2001; Himmerich et al., 2019; Hudson et al., 2007). With psychiatric comorbidities being quite common in bulimic patients it would suggest that there is a neurobiological commonality and pathways in the brain may be altered in similar ways, which

researchers may be able to study in animal models. This could also mean that treatment for bulimia, both pharmacological and behavioural, could be similar to those use for other psychiatric disorders. The questions that will be focused on in this essay are: Are there animal models to portray bulimia nervosa? What is the neurobiology of bulimia nervosa? What are the behavioural or pharmacological interventions? What causes the sex differences in bulimia?

1. Animal Models

It is difficult to create a good animal model for bulimia nervosa due to it being a multifaceted disorder, with environmental, social, psychological and biological factors playing a role in the disorder (van Gestel et al., 2014). Animals are not able to over evaluate their shape and weight which is a key feature of an eating disorder and the sense of loss of control cannot be assessed (N. Bello & Hajnal, 2010; Cooper & Fairburn, 2011). To attempt to replicate the binge eating seen in bulimia a stress-induced hyperphagia model can be used. These rats are allowed periods of restricted eating and then are given free access to food, this is in an attempt to reproduce the self-imposed intermittent fasting and then possibility to binge, something that is done in people with bulimia. This is combined with a foot shock which causes stress. Alternatively, the stress can also be caused by space restriction. These rats then eat a lot when they gain access to palatable foods, which is not seen when only chow was available. These binge like increases in food intake are larger when the shock is used in combination with the restriction compared to the restriction alone (Casper et al., 2008; Hagan et al., 2002; Turton et al., 2017). Other models of binging use different combinations of cycles of restriction and refeeding, stress, limited access to optional foods and eating that is induced by scheduled reinforcement which maintains behaviours (Casper et al., 2008; Corwin & Buda-Levin, 2004). For example, the protocol for a binge eating model, also called the limited access model, by Corwin and Wojnicki used vegetable shortening and provided limited access to it, this resulted in binge eating being induced even in the presence of water and chow. This model can then be used for testing the effect of drugs on food intake behaviours (Casper et al., 2008; Corwin & Wojnicki, 2006).

One of the other main problems with using rats as an animal to model bulimia is the inability for a rat to purge, which is one of the main compensatory behaviours, as mentioned before (Kim, 2012). Some animals are able to regurgitate, such as the gorilla mentioned further, this can be an abnormal behaviour or a normal part of eating and feeding, but these animals are not used for studies (Gould & Bres, 1986; Hill, 2018). To overcome this some studies have used sham feeding models. These rats have a tube that allows the food that has been consumed to be drained from the stomach before it can enter the intestines in order to try to reproduce the purging (Davis & Campbell, 1973). When the food doesn't reach the intestines there may not be the negative feedback signal that is needed to slow down food intake and this also results in a defect in satiety signalling. These rats show binge like behaviour in their food consumption and this may be one of the reasons that people with bulimia binge (G. P. Smith, 1996; Turton et al., 2017). This same increase in intake has been shown in monkeys and dogs (Gibbs & Falasco, 1978; Janowitz & Grossman, 1949). Though these two animals are also able to purge there do not seem to be studies that take advantage of this in order to study bulimia. The sham feeding animal model unfortunately does not offer any insight into the psychopathology of bulimia but does provide some insight into the possible neurobiological causes, and possibly allow for research

into the failed satiety signalling. This allows for pharmacological studies to be done and to target the specific responses to the sham feeding, which may result in more personalized treatments for bulimia (van Vort, 1988). There was a proposed regurgitation model that would use gorillas over the age of 5 as they are then able to regurgitate. Ultimately the researchers believed this model to resemble rumination more than bulimia as there were more similarities with behaviour, motor patterns, treatment, and communication. There were still similarities with bulimia in that there was a lack of eating control, some similar motor patterns and the methods of induction but there was only 38% overlap in characteristics and therefore it was not deemed a useful model for bulimia (Casper et al., 2008; Gould & Bres, 1986).

To understand bulimia, researchers would have to have a better understanding of the neural circuitry involved and the psychopharmacological influences on meal pattering and binge eating in humans, but this is still not fully understood. There is also the limitation of all the psychological factors such as the sense of lack of control, mood, body dysmorphia, and impulsivity (van Gestel et al., 2014). Intake patterns have been studied in humans in an attempt to be able to replicate the pattern and binging in rodents but there are many mechanisms which influence them. There is a lot of variation between people, but bulimic patients eat considerably larger amounts of food regardless of their speed of intake (Casper et al., 2008; Kissileff et al., 2008). As the serotonergic system was suspected to have a role in eating disorders researchers restricted food in rats and observed this system. They found a decrease in the level of 5-HT because of low synthesis and a downregulation of the transporters (Haleem & Haider, 1996; Huether et al., 1997). This is just one of the possible pathways that may be involved in bulimia, and more research has to be done to attempt to elucidate the neural pathways involved in bulimia.

2. Neurobiology of Bulimia Nervosa

The etiology and pathophysiology of bulimia nervosa continues to not be very well understood. To try to better understand the neurobiology of eating disorders researchers are able to use fluid samples to look at the neurotransmitters and other metabolites in the body but they are also able to use more modern techniques of brain imaging to gain insight into the neurological processes (Frank et al., 2019).

The dopamine system has long been researched for its role in reward and addiction, and it also plays a role in eating disorders (N. Bello & Hajnal, 2010). The mesolimbic dopamine pathway includes neurons from the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Berner et al., 2019; Cardinal & Howes, 2005). The greater reward circuitry also involves the ventral caudate and putamen, amygdala, anterior cingulate cortex and orbitofrontal cortex (OFC) (Berner et al., 2019). In a positron emission tomography imaging study researchers suggest that bulimics have disturbances in the brain dopamine functioning and that it is similar to that seen in substance addiction. There was a significant association between striatal dopamine release and binging, as well as vomiting, and the lower the striatal dopamine response to a psychostimulant the greater the frequency of binging in the past month. This disturbance in dopamine function is also seen in people with substance abuse and is suggested to be caused by a downregulation of the dopamine system after a prolonged response to a reward. This would also suggest that the dopamine pathway becomes desensitized (Broft et al., 2012). Other studies

have also found dysregulation in dopamine and its receptors and potentially show hypoactivation in the reward system, which may be the reason for binge eating (Bohon & Stice, 2011; Steinglass et al., 2019). Heal et al. (2017) found that binge eating resulted in an almost 40% reduction of striatal dopamine receptors (D_1), a reduction of D_1 receptors in the medial and lateral caudate putamen, and an increase in striatal μ-opioid receptors. They also tested whether pharmacological intervention could normalize the possible dysregulation in dopamine. Lisdexamfetamine, which increases dopamine efflux, was found to prevent impulsive binge eating in the rats (Heal et al., 2017). What is important to note when trying to investigate the rewarding effect for bulimic patients is that many individuals plan their binging and purging episodes and this may then lead to anticipatory reward, long before the occurrence of the behaviours, instead of only feeling the reward during consumption (Abraham & Beumont, 1982; Peterson et al., 2021; Schultz et al., 1997). In a study done by Avena et al. (2006), rats were provided with 10% sucrose as the only form of food for one hour and then provided with a liquid rodent diet for the remaining 11 hours. There were two groups, the sham feeding, and the real feeding, and both had an increase in dopamine due to the sugar meal, regardless of if the sugar entered the stomach. However, only the real feeding rats had an increase in acetylcholine, which is considered a satiation signal. This satiation signal is attenuated in the sham feeding rats, and these rats are used to mimic the purging that is seen in people with bulimia, as the food is not digested and does not reach the intestines (Avena et al., 2006; Avena & Bocarsly, 2012).

The opioid pathway is also thought to be involved in eating, specifically the hedonic parts of food intake (Berridge, 2009). Will et al. (2004) proposed that the nucleus accumbens and the amygdala were important structures for this pathway, as previous research had found that stimulating the μ-opioid receptors resulted in an increase in energy rich foods but also non-caloric foods. To further investigate this Will et al. used a μ-opioid agonist, DAMGO, and at the same time used a $GABA_A$ agonist in the basolateral or central nucleus of the amygdala. They found that the increase in intake of energy rich foods caused by activation in the nucleus accumbens is dependent on the activation amygdala. When the basolateral amygdala was blocked the intake was comparable to baseline but when the central nucleus was blocked it stopped all food intake, which suggests the structures are very specific (Will et al., 2004). When researchers have used an opioid receptor antagonist, nalmefene, there was a reduction in the binge eating behaviour of the rats (Heal et al., 2017; Vickers et al., 2015). Another pathway implicated in the neurobiology of bulimia is the serotonergic pathway. This pathway is involved in feeding, mood and impulse control, and medications that affect this pathway have been shown to have some beneficial effect on people with bulimia (W. H. Kaye et al., 2005). It is generally believed that patients with bulimia have lower levels of serotonin (5-HT) (Jimerson et al., 1992). When researchers have lowered the level of tryptophan, which is a precursor for 5-HT, it resulted in an increase in depression and desire to binge in bulimic women compared to the control women (W. H. Kaye et al., 2000). When the tryptophan intake was limited in women with a history of bulimia, they had significantly lowered mood, increased body image concerns and reported more loss of control eating. This suggests a reappearance of bulimic ideologies when tryptophan, and therefore serotonin, levels are decreased (K. A. Smith et al., 1999).

Studies have found an association between the appetite hormones and the behaviours associated with eating disorders. In normal healthy controls an increase in ghrelin stimulates hunger and this promotes the ingestion of food. After consumption of a meal ghrelin levels decrease again (Culbert et al., 2016). Some studies have found that though the healthy controls had a decrease in ghrelin after food consumption, those with bulimia had a blunted response. This blunted response may be part of the reason that people with bulimia can experience prolonged meals and binge eating (Monteleone et al., 2003). Not all studies have found that ghrelin levels are increased in bulimic patients post-prandially (Sedlackova et al., 2012). Though the evidence for elevated post-prandial ghrelin levels in bulimic patients is not consistent, there have been consistent results when using a sham feeding paradigm. This focuses on the period before food enters the stomach, when the food is chewed without being swallowed. This is when there is vagal activation, which results in the release of ghrelin. Bulimics consistently had elevated ghrelin secretions compared to controls which is again suggestive to be a reason for the binge eating (Culbert et al., 2016; Monteleone et al., 2010). In contrast to studies finding elevated ghrelin levels in bulimic patients, two studies found that low ghrelin was associated with a higher frequency of binging and compensatory behaviours, but also with the cognitive symptoms, such as the feeling of loss of control, shape fears and fear of gaining weight (Presseller et al., 2021; Troisi et al., 2005).

In addition to the hormones and neurotransmitters mentioned above, there are other possible characteristics of bulimia that can be seen in the neurobiology. Using brain imaging studies researchers suggest that due to abnormal maturation there is a dysfunction in certain frontostriatal circuits. These circuits include the supplementary motor area, the dorsolateral prefrontal cortex, the OFC and the anterior cingulate cortex (Berner & Marsh, 2014). These circuits are involved in self-regulation, habit learning, and reward processing and learning. This dysfunction may contribute to some of the characteristics seen in bulimia, such as the binging and purging (Berner & Marsh, 2014; Lock et al., 2011; Marsh et al., 2011). Stanley et al. (1993) also believe that lateral hypothalamic neurons are involved in food intake. They injected glutamate and found a dose dependent increase in intake, similar results were found when they injected with kainic acid (Glenn Stanley et al., 1993). Some studies have found that cortical thinning and reduced connectivity in the OFC is related to greater symptom severity in bulimia (Westwater et al., 2018) while other studies have found increased connections within the OFC (Wang et al., 2019). It is clear that more research needs to be done into the neurobiology of bulimia and how possible neurotransmitters and structures may be contributing to the pathophysiology of this disease. Information about the neurobiology of bulimia must be known for researchers to be able to properly tailor treatment to the disorder.

3. Pharmacological and Behavioural Interventions

One of the few pharmacological interventions used in the treatment of bulimia is fluoxetine, also known as Prozac, which is a selective serotonin reuptake inhibitor (SSRI) (Milano et al., 2013). The first large scale study looking at fluoxetine as a treatment for bulimia was first done in the early 1990's. A double-blind trial was done with 60 mg per day, 20mg and a placebo in bulimic women. The researchers found that the 60 mg dosage was significantly more effective than the placebo at decreasing the weekly frequency that women were binge eating and purging, 67% vs

33% and 56% vs 5% respectively, compared to their baseline. Additionally, the depression, cravings and eating attitudes and behaviours all improved as well. They also found that the 20 mg dose had some effect, it was between that of placebo and 60 mg (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). More recently reviews have been done to evaluate the effectiveness of SSRI's and other pharmacological treatments for eating disorders. They found that not only did fluoxetine decrease binging and purging but so did other SSRIs like citalopram and sertraline and the SNRI sibutramine (Capasso et al., 2009; Milano et al., 2013). Fluoxetine has also been found to be well tolerated and safe for the use in bulimia, with insomnia being the most common adverse event, occurring in about 20% of patients in one study (N. T. Bello & Yeomans, 2018; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). Topiramate, an antiepileptic agent, is another drug that could be used for the treatment of bulimia but has not yet been approved (Himmerich & Treasure, 2018). It works by increasing GABA activity, modulating the voltage dependent sodium and potassium channels and it blocks the kainite AMPA glutamate receptors (Arbaizar et al., 2008; McElroy et al., 2003). In studies it has led to not only the reduction of binging and purging but also in patients body dissatisfaction and anxiety. Though well tolerated the main side effects were tiredness and some cognitive disturbances. To overcome this researchers recommend starting at lower dosages (Hedges et al., 2003; Himmerich & Treasure, 2018; Hoopes et al., 2003). Topiramate has also been shown to reduce adiposity in humans and rodents. It increases leptin, insulin, anorexigenic neuropeptides and other enzymes that are involved in energy metabolism (Caricilli et al., 2012). These potential weight loss effects should be taken into consideration for patients with bulimia (Muratore & Attia, 2022).

Some patients with bulimia do not respond to any pharmacological treatment and are then classified as non-responders and they will then only use psychotherapy, such as cognitive behavioural therapy (N. T. Bello & Yeomans, 2018). There are some other either less researched or newer methods of possible treatment for bulimia. Oleoylethanolamide (OEA) has been shown to prevent binge eating in rats (Romano et al., 2020). OEA is a lipid derived messenger which is a satiety signal and reduces food intake through noradrenergic and oxytocinergic neurons, specifically through its activation of specific brain areas which includes the paraventricular nuclei (Romano et al., 2020). OEA can be found in certain foods such as oatmeal and nuts but the amount is extremely low, less than 2 µg/g (Payahoo et al., 2018). In studies OEA has been shown to re-establish sensitivity to the rewarding properties of fat in obese mice and have anti-depressant-like effects by increasing the levels of noradrenaline and 5-HT (Romano et al., 2020; Tellez et al., 2013; Yu et al., 2015). The researchers induced binge eating through intermittent restriction/refeeding and palatable food, and the rats were then given frustration stress through a 15-minute exposure to the palatable food placed just out of reach. OEA was systemically administered, through intraperitoneal injection, and there was a dose dependent decrease in binge like eating. The doses used were 2.5, 5 and 10 mg/kg (Romano et al., 2020).Another substance, Lisdexamfetamine (LDX), has been approved for binge eating disorder but not for bulimia. Use of LDX results in an increase of norepinephrine and dopamine in the brain. Studies that have assessed its efficacy have found that binge eating is attenuated and that it is likely due to the activation α_1-adrenergic and D_1 dopaminergic receptors in the brain (Citrome, 2015; Vickers et al., 2015). Dopamine levels increase in a dose dependent manner when patients are treated with LDX (Yun et al., 2017).

Psychotherapy has been shown to have a large effect on patients with bulimia (Svaldi et al., 2019). Cognitive behavioural therapy (CBT) is a type of psychotherapy for bulimia that is often used (Cooper & Fairburn, 2011; P. Hay et al., 2009; Murphy et al., 2010; Shapiro et al., 2007). The use of CBT for bulimia began in the 1980's and the treatment manual has evolved to become CBT-E (enhanced). The treatment focuses on what is assumed to be central to bulimia, the overevaluation of a patients shape and weight with the other elements of bulimia, such as the purging and dietary restraint/restriction, stemming from this (Cooper & Fairburn, 2011). Generally the treatment involves 15-20 sessions over a few months and there is a specific sequence of tasks and experiments that are personalized for each patient with bulimia (Hay et al., 2009). In a meta-analysis of CBT there were large decreases in the rate of binge eating and other compensatory behaviours and depressive symptoms (Svaldi et al., 2019). Though it may seem counterintuitive there has also been research into the effect of physical exercise and dietary therapy (PED-t) as an alternative to CBT (Mathisen et al., 2020). The study compared the two and this focused on patients correcting their eating patterns, self-regulatory processes and changing their idealized evaluations of their self-worth. They found that PED-t was similar to CBT in reducing the symptoms of bulimia (Mathisen et al., 2020). Another treatment method that has been tested in women with bulimia is the use of mirror exposure (Díaz-Ferrer et al., 2015). This is aimed to improve the body dissatisfaction and negative thoughts that may accompany bulimia. In this study bulimic women looked at their bodies in large mirrors. There was a pure exposure group where a participant was alone and asked to verbalize the different areas of their body they were focused on and their thoughts. In the guided exposure group, a therapist used a manual and guided the participants focus to certain areas. Though subjectively measured, women reported reduced dissatisfaction and more positive thought when compared to baseline in both exposure types (Díaz-Ferrer et al., 2015). There are a few other drugs and interventions that are being studied as treatment for bulimia, but they do not yet have known efficacy or safety (Mcelroy et al., 2019). Due to the large sex disparity seen in bulimia it may be possible that treatment methods should be sex specific.

4. Sex Differences

Researchers report a higher prevalence of binge eating and purging in females compared to males. Epidemiological studies have quite a wide variation of sex ratios for bulimia in males vs females, from 1:3 all the way to 1:18 (Austin et al., 2009; Pedersen et al., 2014; Raevuori et al., 2014; Støving et al., 2011). Most research in the field of eating disorders has been focused on women but that results in the potential to miss the differences in how the eating disorders may arise and in how they clinically present in males (Timko et al., 2019). There are differences in how males and females present with an eating disorder, with males not always recognizing symptoms or behaviours and sometimes not meeting the requirements for a specific eating disorder even if they are showing signs of malnourishment and are medically compromised (Coelho et al., 2018; Kinasz et al., 2016; Räisänen & Hunt, 2014). Females are more likely to report weight dissatisfaction, dieting for the reason of weight control and the use of purging. Alternatively, males are more likely to binge eat and use excessive exercise as a means of weight control, and report an increased focus on their muscularity, which may lead to muscle dysmorphia (Murray et al., 2017; Striegel-Moore et al., 2009). Researchers have found this dysmorphia which is

accompanied with disordered eating is comparable to females in terms of the distress and inability to control their behaviours (Murray, Maguire, et al., 2012; Murray, Rieger, et al., 2012).

Not only is there a difference in presentation of the disorder between the sexes but there is also a difference in genetics and gonadal hormones and how they may play a role in the development of eating disorders (Timko et al., 2019). There is an organizational-activational hypothesis about the effect the gonadal hormones have. It states that the exposure to testosterone, or lack of in females, is the primary agent for the organization of the central nervous system. This organizes how the nervous system will respond to certain activations, inhibitions or modulations and results in sexually dimorphic behaviours and anatomical structure and functions (Berner et al., 2019; Kelly L Klump et al., 2017). There is a growing body of research that this difference in organization and sensitivity could contribute to the sex differences seen in certain disorders, including eating disorders. Research by Becker et al. has shown that females have an increased sensitivity to estradiol due to the lack of testosterone during gestation and that the ovarian hormones regulate dopamine release in tissue taken from the dorsal striatum of female rats. It is suggested that estradiol reduces GABA release by binding to estradiol receptors on the GABA neurons, and this decreases the inhibition of dopamine release. This was not observed in tissue from males (Becker & Chartoff, 2019; Becker & Ramirez, 1981). Additional studies are needed in order to better understand the mechanisms behind the organizational effect of hormones and their contribution to the pathophysiology of disorders (Mikhail et al., 2021). Studies have found a significant difference in the effect puberty has on the genetic risk for disordered eating. For males the heritability was stable around 50% pre- and post-puberty. In contrast, genetic factors in females accounted for 0% of the variance in pre-puberty but over 50% during and after puberty. Researchers therefore suggest that there may be a sex specific activation of genetic risk in girls and suggest a focus on the ovarian hormones (K. L. Klump, 2013; K. L. Klump et al., 2012; Young, 2010). This is further strengthened by the fact that the median age of onset for bulimia is 12.4 and this is very similar to the average age for the onset of puberty (Baker et al., 2012; Swanson et al., 2011).

In studies done in rats it has been shown that estradiol has an inhibitory effect on the meal size and food intake and that when the estrogen was taken away it led to changes in the meal size, leading to hyperphagia and obesity (Baker et al., 2012; Brown & Clegg, 2010; Geary & Asarian, 2006). When the estrogen was taken away through the removal of the ovaries in the rats, scientists were able to reproduce normal eating behaviours and meal sizes with injections of subcutaneous estradiol (Geary & Asarian, 2006; Kelly L Klump et al., 2017). It has also been found that women have the largest reduction in their food intake when they are ovulating, which is when estrogen is at its peak (Buffenstein et al., 1995; Lyons et al., 1989). To build on the previously stated heritability, a more recent large-scale study was done by Klump et al. (2018) to investigate what is driving the change in genetic influence on eating disorders during puberty. This was a twin study in girls, and they found that when the estradiol levels were lower there was a stronger genetic influence on binge eating, 69% heritability, and when girls had higher levels of estradiol there was only 2% heritability. This was in contrast to what they had found in their pilot study, but it does suggest a role of estrogen activation during puberty, possibly having a protective effect, and that estradiol may have an effect on the genetic influence on binge eating.

It is also suggestive of a within sex variation in addition to the between sex variation (Kelly L. Klump et al., 2018; Mikhail et al., 2019). Another period in a female's life where there is a large change in hormones is pregnancy. As the pregnancy progresses the estradiol and progesterone levels increase with a peak in the third trimester, after giving birth both hormones decrease (Kodogo et al., 2019). Researchers have investigated how pregnancy impacts anorexia and bulimia. They found that pregnancy had a beneficial impact on the symptoms of the eating disorder (Lasater & Mehler, 2001). Specifically, the symptoms decrease sequentially during the trimesters. By the third trimester the majority of women were considered to be in remission as they had stopped all bulimic behaviours but there is a very high rate of relapse after giving birth (Lacey & Smith, 1987; Lemberg & Phillips, 1989).

It seems the effect of testosterone is not fully understood. In rat studies it appears to depend on the age of exposure and on the level of exposure in utero. One study masculinized female rat brains by exposing them to testosterone in periods of their early development and these rats ate about 10% more than non-masculinized female rats (Bell & Zucker, 1971). More recently Culbert et al. (2018) did a similar experiment. They found that perinatal testosterone altered the brain, and this also masculinized certain behaviours in rats. Unlike in the previous study Culbert found that the female and male rats showed a lower risk for binge eating compared to the untreated control rats, suggesting a protective effect (Culbert et al., 2018). Another study done in women looked at the digit ratio, which is when the second digit is compared to the fourth, which is considered a proxy for the prenatal exposure to testosterone and estrogen. They found that the mean ratio was lowest, which would indicate higher levels of prenatal exposure to testosterone and lower levels of estrogen, in woman with anorexia and was highest in women with bulimia (Quinton et al., 2011). Putting these studies together could suggest that the protective effect against binge eating of prenatal testosterone exposure can be too strong and may result in anorexia, and that if there is not enough testosterone exposure, they are more prone to binge eating which is a key component of bulimia. The researchers also suggest that because females are generally less exposed to prenatal testosterone that is why they have a higher frequency of eating disorders compared to men (Quinton et al., 2011). In research done in adult men it was found that men with lower concentrations of testosterone, done through saliva samples, were associated with having dysregulated eating, specifically reporting having higher levels of loss-of-control eating, binge eating symptoms and more binge eating episodes. This would suggest that testosterone concentrations have an influence on the within sex variation of dysregulated eating in men (Culbert et al., 2020). This also further strengthens the theory that testosterone has a protective effect (Mikhail et al., 2021). Austin et al. did a study investigating sexual orientation and patterns of binging and purging in adolescence. They found that in both males and females those that identified as heterosexual were the least likely to report both binge eating and purging (Austin et al., 2009).

In addition to the gonadal hormones there is the possibility that there are sex differences in other areas of the body. Researchers have found that there is a difference in the stress-related receptors. In studies done in rats, sex differences in glucocorticoid receptor function seem to make female's more prone to dysregulation after they experience a stressful event. Early life stress can also cause sensitization to later responses to stress and this has been linked with the

development of mood and anxiety disorders later (Bangasser, 2013). People with bulimia have been shown to often have psychiatric comorbidities such as mood disorders and anxiety which could mean that this sex difference in receptors may also be related to the eating disorder (Kinasz et al., 2016; Milano et al., 2013). There have also been studies that have found there to be higher rates of assault in women with bulimia which may contribute to the development and or the maintenance of bulimia (Dansky et al., 1997). Meta-analyses have also found a high prevalence of eating disorder development in people who have experienced childhood maltreatment. Those exposed to maltreatment also had significantly earlier age of onset, more severe forms of the illness and binged/purged more than those who were not exposed to maltreatment (Molendijk et al., 2017). Though the research into the area of sex differences, including gonadal hormones, genetics and receptors does not provide a consistent answer, there does seem to be consensus that these factors do have an influence on eating disorders and more research should be done in the field.

Summary

It seems that bulimia shares some physiological and psychological symptoms with other eating disorders, and this gives reason to believe that there may be similar aetiology. This is one of the reasons scientists should continue to investigate eating disorders as this may uncover a common disbalance. Some of the possible pathways implicated in bulimia include the dopaminergic, opioid, and serotonergic neurotransmitters. Furthermore, the appetite hormone ghrelin may play a role and there may be dysfunction in certain structures in the brain. The research about the neurobiology of bulimia is not always consistent and researchers are still searching for the etiology of the disease. The increasing prevalence of obesity has led to quite a bit of research into binge eating, which is also an aspect of bulimia, but the other aspect, purging, still needs more research. Assuming that emesis is not enjoyable it would be interesting to know if any specific hormones or neurotransmitters were released when a patient is purging. It may be that humans also experience the lack of acetylcholine as a satiety signal when they purge, similar to rats.

The sham feeding model is the best model researchers have for bulimia, but it is still not considered a very good representation of the disease. It is difficult to study a disease that has such a large psychological element to it as animals are unable to feel the same emotions that drive a human to do something. Though rats are not able to purge other animals can. For some animals this can be considered a normal behaviour and therefore those animals would not make the best model for bulimia. Many drugs that may help in the treatment of bulimia are still being researched but it is uncertain whether they will prove effective. It is difficult to try to target the medication to something specific regarding bulimia as the neurobiology is still not well understood. However, it does seem that cognitive behavioural therapy is effective and a strong alternative to pharmacological interventions in the meantime. CBT is able to target both the physical eating behaviours in bulimia, the binging and purging, but also the psychological symptoms such as depressive thoughts. It does not seem that scientists are sure why there is such a large sex disparity in bulimia but based on the research it is likely that the gonadal hormones play a role in the pathophysiology of the disorder. It may also depend on when in life a person is exposed to that hormone and which hormone they were sensitized to in the

organization of their central nervous system. In summary, research into bulimia should continue, both in animals and humans, with a focus on the neurobiology so that in the future treatment can become targeted to the disorder.

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