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Review article

Obesity and psychiatric disorders: Commonalities in dysregulated biological pathways and their implications for treatment

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ABSTRACT

Rates of obesity are higher than normal across a range of psychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders. While the problem of obesity is generally acknowledged in mental health research and treatment, an understanding of their bi-directional relationship is still developing. In this review the association between obesity and psychiatric disorders is summarised, with a specific emphasis on similarities in their disturbed biological pathways; namely neurotransmitter imbalances, hypothalamus–pituitary–adrenal axis disturbances, dysregulated inflammatory pathways, increased oxidative and nitrosative stress, mitochondrial disturbances, and neuroprogression. The applicability and effectiveness of weight-loss interventions in psychiatric populations are reviewed along with their potential efficacy in ameliorating disturbed biological pathways, particularly those mediating inflammation and oxidative stress. It is proposed that weight loss may not only be an effective intervention to enhance physical health but may also improve mental health outcomes and slow the rate of neuroprogressive disturbances in psychiatric disorders. Areas of future research to help expand our understanding of the relationship between obesity and psychiatric disorders are also outlined.

Contents

1. Introduction

Investigations into the biological mechanisms associated with psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders have identified several mechanisms specific to each disorder. For example, dysregulation of the neurotransmitter serotonin is associated with major depressive disorder and, to a lesser extent, with several anxiety disorders (Cowen, 2008;

Abbreviations: BMI, body mass index; BDNF, brain-derived neurotrophic factor; CBT, cognitive behaviour therapy; COX, cyclooxygenase; CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamus–pituitary–adrenal; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; PTSD, post-traumatic stress disorder; TNF, tumour necrosis factor.

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Dantzer et al., 2011). Recently, increased attention into the kynurenine pathway has revealed that it is upregulated in major depressive disorder, and interest in its role in other psychiatric disorders such as schizophrenia is underway (Maes et al., 2011b; Myint, 2012; Myint et al., 2011). Other neurotransmitters such as glutamate are linked primarily with schizophrenia, and dopamine with bipolar and psychotic disorders (Abi-Dargham, 2004; Cousins et al., 2009; Seeman, 2009; Steele et al., 2012). Several genetic polymorphisms are also uniquely associated with different psychiatric disorders, such as polymorphisms in the serotonin transporter gene with depression (Kuzelova et al., 2010), and catechol-O-methyl transferase gene polymorphisms with schizophrenia and bipolar disorder (Sagud et al., 2010).

Despite the unique characteristics of each disorder, they share several common dysregulated biological pathways. As illustrated in Fig. 1, these include neurotransmitter imbalances; hypothalamus–pituitary–adrenal (HPA) axis disturbances; dysregulated inflammatory pathways; increased oxidative and nitrosative stress and reduced antioxidant defences; neuroprogression resulting in neurodegeneration, apoptosis, reduced neurogenesis and neuronal plasticity; and mitochondrial disturbances (Altamura et al., 2013; Anderson et al., 2013a, 2013b; Berk et al., 2011; Moylan et al., 2012, 2013; Salim et al., 2012; Vieta et al., 2013). These dysregulated pathways interact significantly with each other, and their translation into specific psychiatric disorders is influenced by other biological mechanisms, environmental factors and genetic polymorphisms.

While it is acknowledged that these disturbances are influenced by genetic and environmental factors, psychological, lifestyle and social influences are also important (Anderson and Maes, 2013; Leonard and Maes, 2012; Lopresti et al., 2013; Maes et al., 2011a). One often overlooked influence concerns obesity. This review provides an overview of the relationship between obesity and psychiatric disorders, similarities in their disturbed biological pathways, and the potential of weight loss interventions not only to improve general health but also to enhance mental health outcomes in psychiatric patients.

2. Is there an association between obesity and psychiatry disorders?

Rates of obesity are greater than normal in psychiatric populations, particularly in women (Allison et al., 2009; McElroy, 2009). For example, Q3 Daumitv et al. (2003) reported that 29% of men and 60% of women with severe and persistent mental illness were obese, compared to 17.7% of men and 28.5% of women in the general population. Dickerson et al. (2006) found that 50% of a female, and 41% of a male psychiatric sample were obese, compared to 27% of women and 20% of men in a non-psychiatric matched comparison group. In a meta-analysis of 15 longitudinal studies, Luppino et al. (2010) concluded that depression was associated with increased rates of obesity. More specifically, a bidirectional association was found between depression and obesity with obesity increasing the risk of depression and prior depression increasing the likelihood of obesity. Several studies have found that abdominal obesity in particular may be characteristic of depression (Carpiniello et al., 2012; Rivenes et al., 2009; van Reedt Dortland et al., 2013).

After controlling for several demographic influences, Petry et al. (2008) concluded that obesity increased the odds of any mood, anxiety, and alcohol use disorder significantly, as well as any personality disorder, with odds ratios ranging from 1.21 to 2.08. In a large, nationally representative sample, Goldstein et al. (2011) found a nearly two-fold age-, race-, and sex-adjusted increased risk of obesity among adults with bipolar disorder versus controls. Obese participants with bipolar disorder also had greater comorbidity with anxiety disorders, longer depressive episodes, and significantly poorer physical and mental health functioning compared to non-obese people with bipolar disorder.

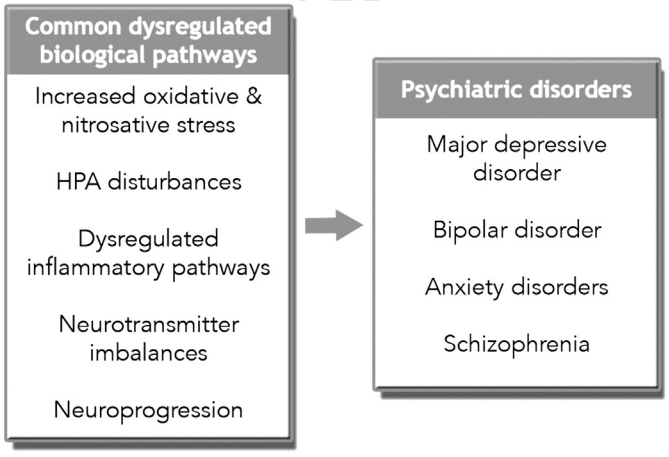

Fig. 1. Common dysregulated biological pathways associated with psychiatric disorders.

3. Possible mediators of the relationship between obesity and psychiatric disorders

Current and past unhealthy dietary patterns are associated both with obesity (Hsiao et al., 2011; Rosenheck, 2008; Schroder et al., 2007) and psychiatric disorders (Jeffery et al., 2009; Sanchez-Villegas et al., 2009; Sanchez-Villegas et al., 2012). Lower rates of physical activity and increased sedentary behaviours are also commonly observed in currently obese (Bailey et al., 2007; Tucker and Tucker, 2011) and psychiatric patients (Azevedo Da Silva et al., 2012; Song et al., 2012) and are also risk factors for the future development of both these conditions. Rates of sleep disorders such as insomnia and sleep apnoea are also increased in obesity and psychiatric disorders (Costa e Silva, 2006; Kalucy et al., 2013; Krystal et al., 2008; Leger et al., 2000), and both obesity and psychiatric disorders are associated with a greater prevalence of cardiovascular diseases (Stanley and Laugharne, 2012), metabolic disorders (Leonard et al., 2012; Rotella and Mannucci, 2013; Yau et al., 2012) and autoimmune conditions (Aballay et al., 2013). Early life trauma, including sexual and physical abuse, has also been identified as a risk factor for the development of obesity (Boynton-Jarrett et al., 2012; D'Argenio et al., 2009; Gunstad et al., 2006) and psychiatric disorders (Breslau, 2002; Chou, 2012).

4. Can psychiatric medications account for the increased rates of obesity in psychiatric populations?

Weight gain is a commonly reported side effect of many psychiatric medications. In a recent meta-analysis, the antidepressants amitriptyline, mirtazapine, and paroxetine were associated with the greatest risk of weight gain, with other investigated antidepressants having only transient or negligible effects on body weight in the short term (Serretti and Mandelli, 2010). However, the effect of each antidepressant may be influenced by several individual characteristics (e.g., sex, BMI, previous medication history, genetic polymorphisms) and generally becomes more evident over the long term (Dent et al., 2012). Weight gain is also a common problem associated with many atypical antipsychotics such as clozapine and olanzapine, and also increases the risk of metabolic disorders such as diabetes mellitus and dyslipidaemia (Dent et al., 2012; Gautam and Meena, 2011; Newcomer, 2005; Rummel-Kluge et al., 2010).

Increasing evidence suggests that genetic factors may be particularly important in medication-induced weight gain. This is supported by monozygotic twin and sibling studies (Wehmeier et al., 2005), and several genetic polymorphisms have also been identified as risk factors for weight gain (Muller et al., 2013). Serotonin and histamine receptors have received most attention as they seem to play important roles in eating behaviour and may contribute to weight gain via their influence on lipolytic activity (Deng et al., 2010). For example, at least 17 studies have reported an association between the 759 T/C SNP in the 5HT2C gene and antipsychotic medication-induced weight gain. This effect

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