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Review

Mechanisms linking depression co-morbid with obesity: An approach for serotonergic type 3 receptor antagonist as novel therapeutic intervention

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ABSTRACT

Despite of the enormous research, therapeutic treatment for depression has always been a serious issue. Even though depression and obesity are individual abnormal health conditions, each act as a triggering factor for the other. Obese individuals are twice prone to develop depression than that of non-obese persons. The exact mechanism how obesity increases the risk for depression still remains an area of interest for research in neuropsychopharmacology. Depression and obesity share some common pathological pathways such as hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of oxidant/antioxidant system balance, higher level of inflammatory cytokines, leptin resistance, altered plasma glucose, insulin resistance, reduced neuronal brain derived neurotrophic factor (BDNF) and decreased serotonergic neurotransmission in various regions of brain. The antidepressant-like effect of 5-HT_3 receptor antagonists through allosteric modulation of serotonergic pathways is well evident from several research investigations belonging to our and some in other laboratories. Furthermore, serotonin regulates diet intake, leptin, corticosterone, inflammatory mechanisms, altered plasma glucose, insulin resistance and BDNF concentration in brain. The present review deals with various biological mechanisms involved in depression co-morbid with obesity and 5-HT_3 receptor antagonists by modulation of serotonergic system as a therapeutic target for such co-morbid disorder.

Contents

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1. Introduction

Depression is potentially life-threatening disorder that affects around 20% of the world population, occur from childhood to late life and have heavy impact on socio-economic status leading disruption of life and if left untreated, can prove fatal (Bondy, 2002). According to the World Health Organization depression would be a second largest global burden in terms of disease severity and disability (Manjit et al., 2001; Nestler et al., 2002). Depression is found to be associated with many co-morbid conditions such as cognitive dysfunction, hypertension, diabetes, obesity and cardiovascular complications (Schulz et al., 2000; Abramson et al., 2001).

Depression and obesity have been known for long time as major public health issues in youths. Data from the National Health and Nutrition Examination Survey estimated 17% of youths ages 2–19 years found to be overweight (Ogden et al., 2006) which remarkably higher compared to just 5% a few decades ago. Several reports have suggested the severity of depression associated with obesity. The exact mechanism for how obesity heightens the risk of depression still remains to be identified (Sharma and Fulton, 2012). Even though obesity and depression re known to be separate health problems of a physical and emotional nature, respectively (Faith et al., 2002), they share some common pathogenesis such as HPA-axis dysregulation, altered plasma glucose, insulin resistance, leptin resistance, pro-inflammatory cytokines, decreased neuronal BDNF and reduced serotonergic neurotransmission (Bornstein et al., 2006).

The clinical antidepressants are reported for resistance against depression co-morbid with obesity in animal models (Isingrini et al., 2010). Interestingly, currently most prescribed antidepressant selective serotonin reuptake inhibitors (SSRIs) exhibits antidepressant effect by functional post synaptic inhibition of 5-HT_3 receptors (Eisensamer et al., 2003). 5-HT_3 receptor antagonists are presently used in the management of nausea and vomiting in chemotherapy of cancer (Mahesh et al., 2005). Some potential 5-HT_3 antagonists have been reported for antidepressant-like effect in several pre-clinical studies (Wolf, 2000; Israili, 2001; Kurhe et al., 2014a). The mechanism of 5-HT_3 receptor antagonists for antidepressant effect is still not clearly exposed. The probable mechanism suggests the allosteric modulation of serotonergic system by post synaptic antagonism of 5-HT_3 receptors and thereby increasing the synaptic neurotransmission of serotonin in various brain regions (Rajkumar and Mahesh, 2010). However, in concerned to the hypothesis of the present review, the data obtained from preliminary experimental studies indicated that 5-HT_3 receptor antagonists such as ondansetron and QCM-4 reversed depression associated with obesity by inhibiting the behavioral and biochemical alterations (Kurhe et al., 2014b,c, 2015). The role of serotonin in the management of depression is well known over the period of time (Owens and Nemeroff, 1994). Serotonin also plays a significant role in modulation of HPA axis hyperactivity, leptin resistance, altered plasma glucose, insulin resistance, inflammatory cytokines, disturbance of oxidant/antioxidant balance and neurogenesis by increasing the expression of BDNF in hippocampus and amygdala regions of the brain. In the present review we have focused on different pathological mechanisms for the co-morbid association of depression and obesity, further suggesting the role of 5-HT_3 receptor antagonists as a novel therapeutic intervention for such co-morbid disorder.

1.1. HPA axis hyperactivity

In the hypothalamus corticotropin releasing factor (CRF) stimulates the synthesis of adreno-corticotropin releasing hormone (ACTH) which in activates the adrenal gland and secretes glucocorticoids. Glucocorticoids exert negative feedback effect on its receptors and inhibit the production of ACTH and CRF (Filip and Stephan, 2004). HPA-axis hyper function is the result of glucocorticoids receptor (GR) resistance (Kendler et al., 2003; Heim et al., 2004) and the negative feedback that elevates CRF (CRF hyperdrive), (Modell et al., 1998; Wolkowitz and Reus, 1999; Zobel et al., 2001).

Stress makes a person fat primarily because of an excessive secretion of the key stress hormone cortisol that is accompanied decrease secretion of growth hormones. Cortisol is catabolic whereas growth hormones are anabolic in nature that leads to accumulation of fat, loss of muscle, decrease metabolic rate and elevates appetite, which all together have the ultimate effect in making a person fatter (Shawn, 2002). The body secretes cortisol in order to cope with stress. Under stress condition cortisol level is elevated. Higher cortisol is observed in obese individuals than non-obese individuals. Cortisol is a hormone in a group of steroids commonly referred to as glucocorticoid. Cortisol has great impact on normal physiological functions of body as it increases blood sugar, blood pressure along with the suppression of the immunity, thus affecting the essential element for adaptation and survival known as "fight or flight" response. The hormones are adrenaline and cortisol is secreted by adrenals upon stimulation from pituitary gland mediated by hypothalamus (Salehi et al., 2005).

Human being has a tendency to react to stressor differently. In the first instant in order to control the situation in case of stress norepinephrine, the "fight" hormone is released predominantly. If stress persists and an individual feels a possible loss of control, then epinephrine, another "flight/anxiety" hormone is released. These autonomic responses cause the heart to beat faster and harder as well as release more free fatty acids (disassembled triglycerides) into the blood stream. Prolong stress makes the individual to feel hopeless, more distressed and feels defeated. This in turn leads to the activation of hypothalamus in the brain that follows a cascade of hormonal pathways finally resulting in the release of excess cortisol from the adrenal cortex. Lipogenesis is elevated by the "defeat" response of stress pathway that leads to visceral obesity, breakdown of tissues, and suppresses the immunity (Jones, 2001; Henry, 1993; Ely, 1995). The hormone cortisol plays an essential role in supplying the energy to body while performing several of the daily physiological activities. Excess cortisol in the blood circulation causes the development of abdominal obesity and obesity is the hallmark for several metabolic and cardiovascular diseases such as diabetes type 2 and hyperlipidemia, respectively (Jean-Pierre, 2006).

1.2. Inflammatory pathway

Data from clinical and pre-clinical reports have shown that obesity increases adipose tissue expression and secretion of pro-inflammatory cytokines. With this concern, treatments that reduce obesity or insulin resistance have a moderating effect of reducing inflammation and associated inflammatory cytokine markers (Ferrante, 2007). Pro-inflammatory cytokine IL-6 have been shown to be higher in overweight children compared to normal weight controls (McMurray et al., 2007) along with the raised C-reactive protein that acts a major biomarker of inflammation and several cardiovascular diseases in overweight persons compared to the non-overweight individuals (Cindik et al., 2005). IL-6 and tumor necrosis factor alpha (TNF-alpha) are reported to be higher in psychiatric patients with major depressive disorder compared with normal controls (Kim et al., 2007). Hence, inflammation and associated cytokines also holds the connecting link for the pathogenesis of depression co-morbid with obesity.

1.3. Leptin hypothesis

Leptin is a peptide known as anti-obesity hormone. In chronic stress leptin levels are suppressed as demonstrated in animal