

Eating Disorders - Neurobiological Correlates

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Abstract: Eating disorders like anorexia nervosa, bulimia nervosa are severe psychiatric disorders with high mortality. The symptomatology of these disorders varies. Understanding the neurobiological correlates of these disorders help in better understanding of the disease and will be helpful in better treatment of these disorders. This article reviews about the neurobiological and brain structural abnormalities seen in these disorders.

Keywords: Anorexia nervosa, bulimia nervosa, CRH, Serotonin, Dopamine.

INTRODUCTION

Eating disorder behaviours can range from dangerous caloric restriction to eating that feels out of control—often combined with unhealthy weight control behaviours, such as self-induced vomiting or laxative abuse. Anorexia nervosa, bulimia nervosa, and binge eating disorder are the most prevalent eating disorders. Usually, Anorexia nervosa occurs commonly in adolescent girls and young women, and adolescent boys and young men may be affected rarely, as may children approach puberty and older women up to menopause [1].

Diagnostically, anorexia nervosa requires low body weight, intense fear of or behaviour that interferes with weight gain, and disturbance in the perception of one's weight or shape. Criteria for bulimia nervosa include persistent preoccupation with eating and actions meant to counteract weight gain like self-induced vomiting, purgative abuse, and alternating periods of starvation, use of drugs as well as overvaluation of body weight or shape [1].

Binge eating disorder involves recurrent binge eating without inappropriate compensatory behaviour.

In India, the exact incidence and prevalence of anorexia nervosa is not known, though there is indirect evidence from various clinics and hospitals that its incidence has been increasing. Persons with Anorexia nervosa and Bulimia nervosa have increased rates of lifetime diagnoses of anxiety and depressive disorders, and obsessive-compulsive disorder [2]. In addition, persons with Anorexia nervosa and Bulimia nervosa are both characterized by perfectionism, low self-directedness, low cooperativeness, obsessive-compulsiveness, neuroticism, negative emotionality, harm avoidance, and traits associated with avoidant personality disorder (PD) [3]. OCD and social phobia are the most common childhood disorders [4].

Neurocircuitry overview

Gut and hypothalamic mechanisms contribute to the regulation of energy metabolism and eating behaviours. Higher-order, corticolimbic systems likely play a role in the path physiology of eating disorders. These systems integrate behaviour with eating and can override homeostatic signals. The insula, anterior cingulate, along with the frontal operculum, processes basic sensory information about food. Nucleus accumbens, putamen, and caudate, as well as the orbitofrontal cortex and amygdala [5], code for the rewarding and motivating value of eating and contribute to approach or avoidance behaviour. Dorsal caudate and dorsal anterior cingulate, lateral prefrontal cortex, and parietal cortex. Weigh the reward value of food and the consequences of consuming it, and they integrate this information with homeostatic and motivational drives to guide eating behaviour. In anorexia nervosa, severely restricted food intake appears to be related to overactive

inhibitory control in combination with underactive reward circuitry. In contrast, dysregulation of both inhibitory and reward drives may manifest in the alternating over- and under-consumption characteristic of bulimia nervosa. Binge eating disorder may be related to altered sensitivity of ventral reward regions.

Findings also suggest that these brain-based differences are linked to temperament traits, such as anxiety and harm avoidance, which persist after remission and may underlie the development of eating pathology.

Neuropeptides

Central nervous system neuropeptide dysregulation can lead on to abnormal function of gonadal hormones, cortisol, thyroid hormones and growth hormone in Eating disorders [6,7]. Animal studies has shown that neuropeptides such as CRH, leptin, beta- endorphin and neuropeptide-Y modifying the feeding behaviours and metabolism [8,9]. Even when anorexia nervosa individuals are of underweight and malnourished they have altered concentrations of CRH, neuropeptide-Y, beta-endorphin, and leptin [10].

Serotonin

Cell bodies of monoamine neurons re located in brainstem and project into cortical and striatal limbic regions. 5-HT disturbances could contribute to appetite dysregulation, anxious and obsessional behaviours and impulse control disorders [11, 12]. Evidences suggest that monoamine function abnormalities occur when people are ill with eating disorders, and it persists after recovery from Anorexia nervosa and Bulimia nervosa [13-15]. Essential amino acid, Tryptophan is available in the diet, is the precursor of serotonin.

Consumption of carbohydrate causes an insulin-mediated reduction in plasma levels of the large neutral amino acids (tyrosine; phenylalanine; valine; leucine; isoleucine) which competes with tryptophan for uptake into the brain. This elevates the plasma tryptophan/large neutral amino acid ratio (TRP/LNAA), and thus brain tryptophan, which rapidly accelerates brain 5-HT synthesis and release.

Restricted diet significantly lowers plasma TRP [16-21], resulting in a decreased plasma ratio of tryptophan to neutral amino acids, and, in turn, a reduction in the availability of tryptophan to the brain.

Despite the abundance of data implicating 5-HT dysregulation in Anorexia nervosa, it remains controversial whether SSRIs are effective in restricting type anorexia nervosa (RAN) individuals. Our clinical experience suggests that RAN respond better to fluoxetine than do binge eating-purging type AN

(BAN) and that some BN individuals can be relatively insensitive to high doses of SSRIs [22]. Severely emaciated person should be hospitalised for supportive medical care and weight restoration. However, relapses are common after discharge.

Dopamine

In anorexia nervosa, symptoms may be caused due to alteration in striatal dopamine. Reduced CSF Dopamine metabolites occur in malnourished individuals with Anorexia nervosa. Striatal DA dysfunction causes altered reward and affect, decision-making, and stereotypic motor activity, executive control and decreased food ingestion in Anorexia nervosa.

Brain Imaging

Imaging studies in eating disorders is categorized. CT (computerized tomography) & MRI (magnetic resonance imaging) is used to diagnose brain structural alterations in individuals with Eating disorders. PET (positron emission tomography), SPECT (single photon emission computed tomography) uses flurodeoxyglucose (FDG) to study glucose metabolism, or a ligand which is specific for a serotonin receptor. FMRI - assess blood flow responses to some stimuli, such as pictures of food. CT reported cerebral atrophy and enlarged ventricles in ill Anorexia nervosa. In Bulimia nervosa, less pronounced structural brain abnormalities were reported. MRI studies in Anorexia nervosa showed larger CSF volumes with deficits in both total grey matter and total white matter volumes and enlarged ventricles. In bulimia nervosa, it showed decreased cortical mass. The parietal cortex mediates perceptions of the body and its activity in physical space [23].

Body image distortion & Appetite regulation

Right parietal cortex lesions result in denial of illness or anosognosia, somatoparaphrenia, misidentification syndromes, but also can produce experiences of disorientation of body parts and body image distortion.

Person with anorexia nervosa and those with lifetime diagnosis of both eating disorders tend to have low mood states and are dysphoric. Abnormal activity in the insula and orbitofrontal cortex (OFC) and mesial temporal, parietal, and the anterior cingulate cortex is seen in person who are emaciated and malnourished due to anorexia nervosa.

5HT_{1A} & 5HT_{2A} receptors

Studies have shown that 5HT (5HT_{1A} & 5HT_{2A}) neuronal system is affected in eating disorders. The exact role of 5HT_{1A} receptor related to behaviour is not known. Some studies have shown that 5HT_{1A} receptor function is associated with aggression [24].

Anorexia nervosa score higher on harm avoidance lower on novelty seeking & reward dependence studies. 5HT_{2A} receptor implicated in modulation of feeding and mood, and SSRI response. 5HT neurocircuitry functions antagonistically with appetite-related DA neurocircuitry.

Increased response in PFC is linked to behavioural inhibition; decreased response is linked to impulsiveness. Lack of impulse control in Bulimia has been linked to 5HT_{1A} receptor binding. (PFC) Reduction in serotonin transporter activity in thalamic-hypothalamic regions. A reduced ventral striatal response to reward has been demonstrated using fMRI. The insular cortex is currently being studied as a specific area of importance for the risk of development of Anorexia.

The insula hypothesis is based on anatomical and clinical research of insula damage in neuroscientific studies including taste, reward, self-image processing. This model, known as nor-adrenergic dysregulation hypothesis proposes that monoamine dysregulation contributes to impaired neuroplasticity in these regions, resulting in body image distortion and impaired feeding behaviour [25].

Dopamine D₂/D₃ receptor

The elevated binding of D₂/D₃ receptors in anteroventral striatum, region which contributes to reward stimuli was found in anorexia nervosa individuals [26].

Monoamine innervation of limbic pathways is complex. It involves many enzymes, messengers, neurotransmitters, pathways and molecules. The 5HT and dopamine function within limbic circuits, but it is not the cause of these disorders per se.

Feeding behavior

The limbic system is responsible for the reward and sensory aspects of feeding behaviour. Insula and orbitofrontal cortex is responsible for feeding behaviour by encoding changes in value of food reward, sensory processing, processing of taste.

Recent findings

Kaye *et al.* reported that the brain circuits of women with anorexia involved in reward processing were less active when they won, but more active when they lost [27]. The occurrence of altered reward system is due to dopamine. Dopamine activity is altered in both anorexia and bulimia. Women with bulimia have weaker response in brain regions which is a part of the dopamine reward circuitry; however the reward circuits in women with anorexia are highly sensitive to food related stimuli [28].

CONCLUSION

Dysphoric temperament is involved in inherent dysregulation of emotional and reward pathways [29] which also mediate feeding, making these individuals vulnerable to disturbed appetitive behaviours. Many factors may act on these vulnerabilities to cause Anorexia nervosa to start in adolescence. Firstly, puberty-related female gonadal steroids or age-related changes may exacerbate 5-HT dysregulation. Secondly, stress and cultural pressures may contribute by increasing anxious and obsessional temperament. Anorexic individuals enter a vicious cycle which leads on to chronicity of this disorder because caloric restriction results in a brief respite from dysphoric mood. Malnutrition and weight loss, in turn, produce alterations in many neuropeptides and monoamine function, in the service of conserving energy, but which also increases dysphoric mood. Thus, those with Anorexia nervosa continue starvation in an attempt to avoid the dysphoric consequences of eating. SSRI administration does not appear to be effective in counteracting 5-HT disturbances in patients with Anorexia.

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