2.1 EPIDEMIOLOGY OF DEPRESSION

Depression is a well-known and frequently used expression in our everyday lives. In general it is used to describe prolonged low mood, or a reaction to unpleasant life events. It is predicted that by the year 2020, depression will be the second leading cause of the global disease burden (Kapoor et al., 2009). The rate of depression in Indian preschool children has been estimated to be about 0.3% in community and 0.9% in the clinical settings. In the school age children in the community it is about 2% and among adolescents about 5% of the community. Among the hospitalized children and adolescents the rate of major depression is much higher than in community with as many as 20% children and 40% adolescents affected (Dhavale, 2001). According to a report by Arun and Chavan (2009) teen suicide rates have trebled in past 25 years and about 40% teens suffer from the anxiety. The long-term consequences of which, lead to depression in adolescence. In a study by Madhav (2001) national prevalence rates for all mental disorders was observed to be 65.4 per 1000 population. Prevalence rates for schizophrenia, affective disorders (depression), anxiety neurosis, hysteria and mental retardation were 2.3, 31.2, 18.5, 4.1 and 4.2 per 1000 population respectively. Gupta et al. (2006) stated that the prevalence of depression in various samples in India varies from 1.6% to 3.8% and these depend on the source of sample, the diagnostic criteria and screening instruments used. Prevalence of depressive symptoms in general population in old age has been estimated in different surveys and ranges between 13-20% (Khandelwal, 2001). Rajkumar et al. (2009) studied the prevalence of depression in elderly Indian subjects and found that prevalence of geriatric depression (ICD-10) within the one month from study was 12.7%.

2.2 SUB-THRESHOLD AND SUB-CLINICAL FORMS OF DEPRESSION

A significant portion of the population suffers from low mood, and although besides serious subjective suffering this cause’s severe work, interpersonal and marital
dysfunction, their state is not diagnosed as depression because their symptoms do not reach the diagnostic criteria. They either do not satisfy the criteria in the number of symptoms or in the duration of symptoms, while the severity of the symptoms reaches the level observable in diagnosed patients. Also, in many cases depression presents primarily with physical symptoms, with very mild mood disturbances or altogether without any major mood problems, in which case patients are never referred to psychiatry. These patients are significant in number, and based on several, long-term follow-up studies, these states are often intermediary states later leading to the development of major depression. Several scientists and clinicians described sub-threshold forms of depression resulting in several syndromes each grabbing a different aspect of sub-threshold depression.

Subclinical forms of depression have been described very long ago: Paškind in 1930 already noted minor affective symptoms recurring on a cyclical basis as well as neurovegetative signs and symptoms such as anergia, headaches, insomnia, sexual disturbances, gastrointestinal disturbances, palpitations, and anxiety symptoms (Akiskal, 1997; Pezawas et al., 2003). Although most people suffering from sub-threshold depressive syndromes never seek medical help, patients presenting with depressive symptoms not meeting diagnostic criteria of any DSM-IV defined depressive disorders are still fairly common outside psychiatric practices and the degree of impairment in some of these cases is comparable to major psychiatric disorders, causing substantial dysfunction, work impairment and social disability (Rapaport and Judd, 1998; Angst and Merikangas, 2001). Besides limitations in general role and work function, people suffering from sub-threshold depression report significantly increased health service use and need for public assistance (Judd et al., 1997; Angst and Merikangas, 2001). The need for treatment is also often comparable to that in case of major mood disorders (Maier et al., 1997). Sub-threshold depression is associated with significant psychological distress, disability and poor health perception (Angst and Merikangas, 2001; Rucci et al., 2003) and also leads to a significant decrease in psychosocial function (Judd et al., 1996; Judd, 1997; Angst and Merikangas, 2001). Sub-clinical depression patients also have a high
risk of developing major affective disorders in the future; more than 25% of sub-threshold depression patients develop major depression in the next 2 years (Sherbourne et al., 1994; Kendler and Gardner, 1998; Angst and Merikangas, 2001). Other studies indicate that sub-syndromal depression can be observed during the course of illness in case of major depression patients where sub-syndromal depressive symptoms may alternate over time with major depressive and minor depressive symptoms (Judd et al., 1998). Sub-syndromal depression shows a great similarity to major depression with respect to family aggregation (Judd, 1997; Lewinsohn et al., 2003) and treatment response (Rapaport and Judd, 1998), thus suggesting that less severe forms of depression are a part of a broad spectrum of depressive disorders. In spite of the fact that major mood disorders carry the highest risk of suicidal behavior, many studies have shown that more suicide attempts are associated with sub-threshold depression (25.8%) than with major depression (11.1%), and sub-threshold depressions cause similar impairments as major depression such as increased use of medical and mental health services, greater number of sick days, impairment in social and occupational functioning, and in addition, sub-clinical depressive symptoms are also more prevalent than major mood disorders (Judd et al., 1997; Borrelli et al., 1999; Angst and Merikangas, 2001). Depression is a heterogeneous phenomenon and current DSM-IV categories defining different types of depressive disease fail to cover all forms of this disorder, leaving a substantially large group of people suffering from sub-threshold depressive symptoms without a proper medical diagnosis. Several categories have been proposed to cover those people who complain of depression but do not meet the criteria for major depression (Maier et al., 1997). Dysthymic disorder is characterized by a reduced number of symptoms showing a minimal duration of 2 years. Minor depression is defined by a shorter minimal episode length and a smaller number of symptoms as major depression. However, sub-syndromal symptomatic depression is a less severe form of depression than dysthymic disorder and minor depression. Recurrent brief depression (Judd et al., 1997; Maier et al., 1997) is a disorder characterized by episodes occurring about once a month for at least one year, meeting the symptomatic criteria for a mild to severe depressive episode, but lasting for less than 14 days (usually 2-3 days). Recurrent brief depression may occur spontaneously
or can be triggered by mild psychosocial stress (Pezawas et al., 2003). Masked depression patients present primarily with physical symptoms and therefore this phenomenon can also be related to sub-syndromal depressive disorder without predominant mood disturbances (Rihmer et al., 1983; Maier et al., 1997). Sub-syndromal depressive disorder (Judd et al., 1994) is defined as the manifestation of at least two symptoms usually associated with depression for at least two weeks with or without depressed mood. Most common symptoms of sub-clinical depression include insomnia, feeling tired all the time, recurring thoughts of death, trouble concentrating, significant weight gain, slowed thinking and hypersomnia. One half of the patients (54.1%) reports only two symptoms. It is fairly common in the population (one year prevalence is 11.4%), and is associated with significant social and work impairment. This condition has two subtypes. Sub-syndromal depressive disorder with mood disturbance has a one year prevalence of 3.4%. Sub-syndromal depressive disorder without mood disturbance has a remarkably high prevalence in the population (one year prevalence is 8.4%), (Judd et al., 1994) and it covers people suffering from depression without associated mood disturbances, who thus never seek the right professional help. Sub-syndromal depressive disorder shows relationship with masked depression in that its leading symptoms are primarily physical and vegetative: insomnia, morning hypersomnia, fatigue, headache, abdominal pain, hyperventilation, palpitation, erectile failure (Rihmer et al., 1983; Akiskal, 1997). This disorder is also similar to atypical depression because its symptoms include weight gain (rather than weight loss), hypersomnia (as well as insomnia) and slowed thinking (Judd et al., 1994).

Earlier studies conclude that this disorder is a dangerous, hidden problem in the population because neither the patients nor the physicians discover that the symptoms have to do with depression (Judd et al., 1994). This underlines the importance for establishing proper screening tools for the sub-clinical forms of depression and the need for better understanding of the biological background of these sub-clinical forms of depression and their etiological and biological relationship to major mood disorders.
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2.3 NEUROBIOLOGICAL BASIS OF DEPRESSION

Mood disorder is probably the most frequent and prevalent form of mental illness (Nestler et al., 2002) and is almost twice more common in females than in males. Depression in current psychiatry is viewed as a heterogonous syndrome consisting of several disorders with distinct causes and patho-physiologies (Nestler et al., 2002; Aan het Rot et al., 2009).

2.3.1 NEUROANATOMY OF DEPRESSION

Depression involves complex central nervous system processes. Several brain areas are implicated in the background of the diverse symptoms associated with depression. We have very little knowledge about neural circuitry underlying normal and abnormal mood but it is well known that many brain regions play a role in mediating the symptoms of depression. Brain imaging and autopsy studies have demonstrated the role of several brain areas, including the prefrontal cortex, cingulate cortex, hippocampus, striatum, amygdala and thalamus (Nestler et al., 2002). These areas play different roles in the manifestation of depressive symptoms. The neo-cortex and the hippocampus are responsible for the cognitive aspects of depression (memory impairments, feeling of worthlessness, feeling of guilt, doom, suicidality), the striatum and amygdala are responsible for mediating anhedonia, anxiety and reduced motivation. Hypothalamus plays a role in the neuro-vegetative symptoms, such as changes in sleep, appetite and energy and loss of sexual interest (Nestler et al., 2002). The key changes observable in depression involve the disturbance of emotions. There are four main areas in the brain which play an important role in the regulation of emotions: the prefrontal cortex (PFC), the anterior cingulate cortex, the hippocampus and the amygdala. The prefrontal cortex is responsible for behaviors related to reward or punishment, it contains representations of goals and the behavioral responses needed to reach those goals. The PFC is thus involved in both appetitive and avoidance behaviors. The anterior cingulate cortex is implicated in the integration of attentional and emotional inputs. The hippocampus plays a central role...
in learning and memory, also involving emotional learning, while the amygdala is crucial in processing stimuli with emotional significance as well as coordinating responses. Studies investigating the role of these areas in depression have been expanding in recent years (Thase, 2005).

Areas related to information processing are also thought to play a role in the neurobiology of depression. Characteristic cognitive alterations can be observed in case of most depressed patients, such as interpretation of experiences from a negative perspective, and negative memory bias. Cognitive problems are also evident in more severe cases of depression, such as poor concentration, compromised problem-solving skills and decreased ability for abstract thinking. These neuro-cognitive changes involve the prefrontal cortex, the hippocampus and other structures in the limbic system (Thase, 2005).

Nowadays the role of sub-cortical structures have gained more attention (n. accumbens, hypothalamus, amygdala) because of their contribution to such symptoms of depression as motivation, sleep, appetite, energy, circadian rhythms and anhedonia (Nestler et al., 2002). Anhedonia, decreased interest and loss of mood reactivity is related to neural circuits involved in anticipation and consummation of rewards involving the thalamus, hypothalamus, nucleus accumbens and prefrontal cortex (Thase, 2005). Thus the impairment of brain reward pathways is also thought to play a role in the background of depression (Nestler et al., 2002).

Psychomotor retardation, another characteristic symptom of depression, points to the dysfunction of sub-cortical circuits connecting the thalamus, basal ganglia and striatum (Thase, 2005). The hypothalamus mediates various neuroendocrine and neuro-vegetative functions. It has been studied in relation to depression mainly because of its role in the HPA axis. Other hypothalamic nuclei and neuro-peptide transmitters received less attention although they play a crucial role in mediating sleep, appetite, circadian rhythm
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and sexual interest, which are among the main symptoms of depression (Nestler et al., 2002).

The amygdala plays a role in fear and fear conditioning, and also in conditioned responses for rewarding stimuli, and as a part of a larger circuit formed by the nucleus accumbens, bed nucleus of stria terminalis and other regions it also plays a role in emotional memory (Nestler et al., 2002). Monoaminergic neurons (Locus coeruleus, raphe nuclei part of the ascending serotonergic system) also play important roles in several symptoms associated with depression (sleep, circadian rhythm, memory, cognitive functions, eating, etc), and in addition they modulate all above areas through their projections and receptors expressed in these areas (Thase, 2005).

2.4 NEUROTRANSMITTERS

Several neurotransmitter systems play a role in the background of depression. The catecholamine and later the monoamine hypothesis was the first attempt to link depression to specific biochemical disturbances in the brain. Although this hypothesis has been substantially revised, noradrenalin and serotonin are still thought to play a central role in the neuro-chemical background of depression.

Decreased central noradrenergic activity has been observed in the brain of depressed patients, with a dissociation of noradrenergic activity in certain brain areas and thus increased noradrenergic function in the medial forebrain bundle (Thase, 2005). Originally the catecholamine hypothesis linked depression to the low noradrenalin levels in the brain. Several antidepressants, such as imipramine, by inhibiting the reuptake, increased noradrenalin levels in synapses, while MAO inhibitors increased synaptic noradrenalin levels by inhibiting the enzyme responsible for noradrenalin degradation. Reserpin, which depletes monoamines, leads to an increase in depressive symptoms. Some studies showed that some depressed patients show decreased levels of MHPG (3-methoxy-4-hydroxyphenylglycol), the main metabolite of noradrenalin (Andreasen and
Black, 1995). Among other effects, tricyclic antidepressants inhibit noradrenalin uptake, while some new antidepressants inhibit noradrenalin uptake selectively. Yet others antidepressants have α2-antagonist properties. Other neurotransmitters also play a role in depression. Serotonergic dysfunction in depressed patients has also been revealed by research (Thase, 2005). Newer antidepressants act through the inhibition of the serotonin transporter, thus increasing synaptic levels of serotonin. Patients with severe depression also show decreased levels of 5-HIAA, which is the main metabolite of serotonin (Andreasen and Black, 1995).

Fig 2.1: Serotonergic pathway in human brain (Andreasen and Black, 1995)

It has long been described that abnormal serotonergic function plays a role in affective disorders since serotonin transporter binding is reduced in mood disorder patients, a
result interpreted as a compensatory response to central serotonin deficiency (Owens and Nemeroff, 1998). It has also been demonstrated in imaging and post-mortem studies that depressed individuals have reduced serotonin transporter expression in the brain (Lira et al., 2003).

Fig 2.2: Schematic illustration of serotonergic neuron with its cell body in the raphe nuclei (left) and axonal projection to a region with postsynaptic receptors (right). The major steps in synthesis, release and degradation of serotonin are indicated (Andreasen and Black, 1995)

Results from knock out mice studies also point to the role of serotonin in depression. Mice homozygous for the null mutation (5HTT-/-) exhibit reduction in dorsal raphe firing as well as desensitization and down-regulation of somatodendritic 5HT1A auto-receptors. Postsynaptic 5HT1A receptors are also reduced in the frontal cortex, amygdala, septum and hypothalamus. The binding density of 5HT2A receptors is increased in the hypothalamus, while 5HT2C receptor density is increased in the amygdala (Holmes et al., 2003). The impairment in dorsal raphe nucleus function leads to reduced serotonergic function and might play a causative role in depression (Lira et al., 2003). These results also have implications for the use of serotonergic antidepressants during pregnancy, since inhibition of the serotonin transporter at critical periods of development might increase vulnerability for affective and anxiety disorders (Lira et al., 2003; Alexandre et al.,
2006). The acetyl-cholinergic system has also been implicated in the background of depression. The increase of cholinergic activity decreases monoaminergic brain activity. Cholinergic agonists increase depressive symptoms, like dysphoria and psychomotor slowness (Andreasen and Black, 1995). Tricyclic antidepressants have anticholinergic properties as well. Several neuro-physiological differences are observable in depression. Most studies focused on sleep EEG differences in depressed patients: decreased REM latency, decreased slow-wave sleep, and increased REM density which coincides with insomnia, a frequent symptom of depression (Andreasen and Black, 1995).

2.5 NEURO-ENDOCRINE FUNCTION

According to Andreasen and Black (1995) there are differences in neuro-endocrine function observable in depression. Metabolites of cortisol are increased in the urine of depressed patients and there is an increased plasma cortisol level. Dexamethasone suppression test, an indicator of the hypothalamus-hypophysis-adrenal gland system also shows characteristic differences in case of depressed patients. Suppression of the normal cortisol response after dexamethasone provocation can be observed in depressed patients. The differences in the function of other neuro-endocrine systems indicate that the difference is at the level of hypothalamic regulation.

Many modern hypotheses dealing with the neurobiology of depression investigate the dysregulation of the HPA axis and hippocampus, and focus on CRF, glucocorticoids, BDNF and cREB. The hypothalamus-pituitary-adrenal axis is activated in response to acute stress and as a result the level of glucocorticoids is increased which, among other effects, act on different brain regions thus influencing behaviour (Nestler et al., 2002). Increased levels of glucocorticoids under normal conditions inhibit HPA activity through their action on the hippocampus, and also promote certain cognitive abilities. Excessive activation of the HPA axis can be observed in about half of depressed patients, some exhibit increased cortisol production and decreased DST (dexamethasone suppression test), and in some patients CRF is hypersecreted (Nestler et al., 2002; Bao et al., 2008 ).
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The role of the HPA hyperactivity in depression is not fully understood, but current hypotheses suggest that elevated glucocorticoid levels over sustained time periods might be toxic to hippocampal neurons, which might contribute to the cognitive impairment observable in depressed patients. Due to this damage the inhibitory control of the hippocampus on the HPA axis is decreased. Increased HPA activation might also contribute to depression by way of enhanced CRF transmission in the hypothalamus, since central administration of CRF causes symptoms similar to depression, such as increased arousal, decreased appetite and sexual behavior and increased heart rate (Bao et al., 2008).

Furthermore, chronically increased glucocorticoid concentration markedly alters functions mediated by 5-HT receptors (Bagdy et al., 1989; Calogero et al., 1989). It is still not known, however, whether HPA abnormality is the cause of depression or is secondary to some common cause. It has been suggested that increased CRF function and increased activity of the HPA axis observed in depression and anxiety disorders might be related to the dysfunction of serotonergic regulation. Agents increasing serotonin levels and selective 5HT1A, 5HT2A, 5HT2C agonists activate CRF secretion of hypothalamus (Calogero et al., 1988; Bagdy et al., 1989), and the almost exclusive role of the hypothalamic para-ventricular nucleus in these responses has also been shown (Bagdy and Makara, 1994; Bagdy, 1996).

2.6 NEUROTROPHIC FACTORS

The role of neurotrophic factors have also been implicated in the background of depression. These factors not only regulate neuronal growth and differentiation during development but in case of adult cells they are also regulators of activity and survival. It is postulated that deficiency in neurotrophic support may play a role in hippocampal pathology and thus depression. Most of recent research focuses on BDNF which is decreased by chronic and acute stress in a process mediated partly by glucocorticoids and stress-induced changes in serotonergic neurotransmission in the dentate gyrus and the
hippocampus. Antidepressants can increase BDNF levels suggesting that antidepressant induced upregulation of BDNF might play a role in repairing stress-induced hippocampal damage and also in protecting vulnerable neurons. In the action of BDNF cREB is involved (cAMP response element binding protein). cREB induces the BDNF gene and cREB levels are increased by all antidepressants in several brain regions including the hippocampus (Nestler et al., 2002).

2.7 DEPRESSION AS A HEALTH PROBLEM

Depression not only causes mental anguish, but also impairs some of the most fundamental biological functions, such as sleep, appetite, sexual activity and metabolic and immune functions (Rost, 2009). As a consequence, depression is related to, and is seen as a risk factor for a number of chronic and critical illnesses, such as diabetes, cardiovascular disease and cancer (Patten, 1999). Depression also frequently accompanies other psychiatric disorders, such as schizophrenia, anxiety disorders, drug and alcohol dependence and personality disorders (Enns et al., 2001; Otte, 2008). As well as being a risk factor for a number of chronic illnesses, depression also increases patient’s susceptibility to suicidal ideations and actual acts of suicides. Suicide rates among patients with depression are disproportionately higher than the general population, higher even than rates for other psychiatric conditions (Bostwick and Pankratz, 2000). About two thirds of patients with depression show suicidal ideation, and 10 -15 percent complete suicide. Although depression seems to be more common in women, and although women have more suicide attempts than men, the rates of completed suicide are about 4 times higher in men (Hawton and Van Heeringen, 2009). The higher rates of completed suicide in men have usually been attributed to the differences in suicide methods used by men and women: men usually tend to use more fatal and effective methods, such as a gun or incarceration.

2.8 RELATIONSHIP BETWEEN DEPRESSION AND OBESITY

A growing number of researchers have investigated the relationship between depression and obesity. Depression and obesity share common health problems such as
hypertension, dyslipidemia, diabetes, cardiovascular disease, and increased mortality rates although a causal link has not been established between these two disorders. Surveys conducted in the U.S. have found positive associations between depression and obesity among women but not among men (Istvan et al., 1992; Palinkas et al., 1996; Carpenter et al., 2000). Some researchers have suggested that the association between depression and obesity occurs through multiple mechanisms rather than a single or unidirectional pattern of association (Faith et al., 2002). In contrast, other investigators contend that depression and obesity likely co-occur by chance given the high prevalence of both of these disorders (McElroy et al., 2004). Researchers also speculate that depression may precipitate obesity and obesity may increase symptoms of depression (Chapman et al., 2005). Findings from studies have demonstrated that weight gain is a common side effect of treatment for depression (Devlin et al., 2000) and, furthermore, medications used to treat obesity related complications frequently exacerbate depressive symptoms (Brown, 1998; Tyrovolas et al., 2009).

Divergent views exist however, among researchers about whether a relationship exists between depression and obesity (Friedman and Brownell, 1995; Faith et al., 2002). A positive relationship between depression and obesity was found in community-based studies (Istvan et al., 1992; Carpenter et al., 2000; Roberts et al., 2000; Roberts et al., 2002). In contrast, many studies with similar methodology found no significant associations between depression and obesity (Atlantis and Baker, 2008; Rihmer et al., 2008).

Inconsistencies in previously published studies on the association between depression and obesity may arise because of variations in methodology (Carpenter et al., 2000). In fact, results from many aforementioned studies came from clinical trials without control groups or from community samples not representative of the population and subject to selection bias. These factors, therefore, may contribute to inconsistencies among studies associating depression and obesity (Carpenter et al., 2000). Goodman and Whitaker
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(2002) and Onyike et al. (2003) contend that depression and obesity may not always co-occur, which may account for inconsistencies in prior studies.

The relationship between depression and body mass index (BMI) is also not clear and study results remain inconsistent (Anderson et al., 2006). Nevertheless, Pine et al. (2001) found a positive association between childhood depression and increased BMI scores in adults wherein, participants with a history of childhood depression had higher BMIs (26.1 ± 5.2) as adults, compared to persons not depressed (24.2 ± 4.1; t (175) = 2.7). From their study of women and men with anxiety and depressive disorders (N = 310), (Anderson et al., 2006) reported that 32% (n = 98) of depressed women had higher BMI scores and were more likely to have yearly increases in BMI scores than did women who were not depressed (n = 93). In their study of the relationship between depression and BMI, Onyike et al. (2003) discovered a stronger association between depression and higher BMI scores (≥ 40) compared to depression and lower BMI scores (<40). Unlike the previous studies, Ross (1994) found depression associated with increased BMI only among well-educated persons. While inconsistencies exist among studies on the relationship between depression and BMI, there is plausible evidence that an underlying association between depression and elevated BMI may exist (Saules et al., 2009).

2.8.1 GENDER DIFFERENCES IN RELATIONSHIP BETWEEN DEPRESSION AND OBESITY

Some researchers have suspected the relationship between depression and obesity differs among women and men. One study found that obese women experienced a 50% increase in the lifetime prevalence of depression in contrast to men who were obese (Becker et al., 2001). Furthermore, analysis of data from the 3rd National Health and Nutrition Examination Survey (NHANES III) conducted by Onyike et al. (2003), revealed that obesity was related to the previous month history of depression in women but not men. Carpenter et al. (2000) observed a strong correlation in the co-occurrence of depression and obesity in women and an inverse relationship in the co-occurrence of depression and
obesity in men. Results from this study showed a 37% increase in depression in obese women compared to a 37% decrease in depression in obese men (Carpenter et al., 2000). On the other hand, central obesity and a high waist to hip ratio was associated with greater risk for depressive symptoms and increased use of antidepressants in men but not in women (Rosmond and Bjorntorp, 2000). Contrary to findings from these studies are results from a study by Dong et al. (2004) which found a significant association between depression and obesity among both women and men.

2.8.2 ROLE OF EATING DYSREGULATION IN THE ETIOLOGY OF DEPRESSION AND OBESITY

From a psychiatric point of view, it could be expected that both overweight and underweight are associated with depression. According to the DSM-IV in which the diagnoses of mental disorders are described, eating problems (eating too much or eating too little) and changed physical activity (increased or decreased) both constitute core symptoms of a major depressive disorder. Even though an increase in food intake might be more likely than a decrease in food intake, there is little evidence to support this assumption. Furthermore, even though a decrease in food intake might occur less frequently, it might still affect large numbers of people since depression is such a prevalent disorder.

Kaplan and Kaplan (1957) proposed that eating serves to reduce anxiety (such as alcohol helps to reduce anxiety to the patients with substance abuse). Food addictions caused by anxiety, and all addictive substances, including food, are tranquilizers that serve to mask anxiety. “The reason most diets don't work is because they treat the symptom (eating) rather than the cause anxiety” (Kaplan et al., 1994). In contrary to the anxiety reduction hypothesis in obesity, Ruderman (1983) have found that obese individuals ate significantly less when they are highly anxious than when they feel only mildly anxious. His findings showed that obese people consume the maximum quantity of food when they are at moderate level of anxiety. Later eating was regarded as a copying behavior to
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make the individuals feel better and to avoid feeling and expressing negative emotions (Bekker and Boselie, 2002). Significantly higher alexithymia was reported also in binge-eater obese female in the study of (Pinaquy et al., 2003). The findings indicated that obese women who have difficulty identifying and communicating their feelings have a tendency to eat in response to emotions.

Anorexia nervosa: Emotional functioning deficit in anorexia nervosa is characterized also by avoidance in coping with conflicts or responding to emotions (Pinaquy et al., 2003). Kucharska et al. (2004) have found that women with anorexia nervosa had difficulties to recognize emotion in faces, which was most marked for negative emotions. It was reported (Bruch, 1962; Geller et al., 2000) that anorexic patients have a tendency to avoid negative emotions, and to inhibit negative emotion expression, especially they are prone to suppress anger. Blinder et al. (2006) observed that patients with anorexia nervosa reported mood disorders (94% of the cases unipolar depression) and anxiety disorders (56 % of the cases). Godart et al. (2006) showed that generalized anxiety is the most frequent disorder in anorexia nervosa and it appears to be one of the main predictive factors for major depressive episode. Kaye et al. (2004) suggested that anxiety disorder appears in childhood and it presents before the onset of the anorexia nervosa. This supports the possibility of anxiety being a vulnerability factor for developing anorexia nervosa. Using the Toronto Alexithymia Scale (TAS20) higher prevalence of alexithymia was found in the anorexic population than among substance abusers, chronic disease patients or general psychiatric out-patients (Bourke et al., 1992). Based on this result it seems that alexithymia is associated with the pathology of anorexia nervosa. Montebarocci et al. (2006) showed that although patients with anorexia reported higher alexithymia compared to controls it was mainly related to negative affect, the significant group differences had disappeared when alexithymia was controlled for anxiety and depression.

2.9 GENETIC BACKGROUND OF DEPRESSION

It has long been observed that just as several other types of psychiatric disorders, depression also tends to aggregate in families and tends to be inherited. The heritability
of mood disorders has also been supported by several studies. The focus of recent studies is the identification of specific genes which play a role in the background of depression. Genetic studies also reveal that there is substantial genetic similarity between bipolar and unipolar depression, although the biological and genetic background seems to be stronger in bipolar depression (Kelsoe and Niculescu, 2002; Cichon et al., 2009; Smith et al., 2009).

The lifetime prevalence of unipolar major depressive disorder is at least 10% and the heritability based on twin studies is between 40 and 50% (Nestler et al., 2002; Levinson, 2006; Murphy-Eberenz et al., 2006). The relative risk of first degree relatives of major depressive patients to develop depression is 2-3 as compared to the general population (Levinson, 2006). The mode of inheritance has not been delineated so far, and several environmental factors such as childhood abuse and neglect and early life stress also play a role (Luby and Belden, 2008). The familial, inherited nature of depression has been observed long ago, although familial aggregation does not always infer a genetic definition, because role patterns, learned behaviors, socioeconomic and cultural environment and physical factors influencing the emergence of depression are also familial (Andreasen and Black, 1995). Studies of familial aggregation, however, argue for a genetic basis of depression: the frequency of depression (both unipolar and bipolar) was significantly higher among first degree relatives of patients. Twin and adoption studies also support these results. Linkage studies also point to the same direction (Kelsoe and Niculescu, 2002).

2.9.1 GENETIC LINKAGE STUDIES

According to data from twin studies, genes are responsible in 50-70% of the etiology of mood disorders, while the remaining 30-50% is due to environmental factors, meaning that inheritance is responsible for a predisposition or increased risk (Cichon et al., 2009). Genetic studies focusing on the background of depression might utilize several approaches. An alternative to the study of mechanism-based candidate genes is the positional cloning strategy—the systematic study of the genome, either with genetic
linkage studies of informative pedigrees followed by association studies of candidate regions (e.g., using very dense maps of single nucleotide polymorphisms) or systematic genome-wide association studies. The latter have not yet been attempted for depression, but several linkage studies have been reported for MDD and related traits. A comparison of these studies illustrates the diverse strategies available for this problem (Cichon et al., 2009).

In genetic studies a greater attention is paid to bipolar disorder than unipolar form of depression. Several genes or DNA sequences have been implicated as related to bipolar disorder (4p16, 4q35, 6q, 8p, 10p12, 10q25, 12q23-24, 13q32, 16p13, 17q, 18p11, 18q21, 18q22-23, 21q22.3, 22q11-q12, Xq26-q28) (Alaerts (Alaerts and Del-Favero, 2009) and Del-Favero, 2009, (Mick and Faraone, 2009).

The studies used 9 to 10 cM microsatellite marker maps, except that the (Abkevich et al., 2003); (Camp et al., 2005) analyses are from the same study, which used a 5cM map. The clinical characteristics of an additional industry-sponsored study of 470 recurrent MDD (MDD-R) affected sibling pairs (ASPs) have been published (Farmer et al., 2004). In the three MDD scans, approaches to analysis have varied. Holmans et al. (2004) analyzed a single diagnostic model (MDD-RE, with age at onset less than 31 for probands and 41 for other cases) with one primary linkage analysis (multipoint allele-sharing analysis using ALLEGRO [(Gudbjartsson et al., 2000)]) and empirical genome-wide p-values. Abkevich et al. (2003) and Camp et al. (2005) published separate analyses of the same linkage study of large Utah pedigrees selected for having multiple MDD cases. Abkevich et al. (2003) considered all MDD and BD cases as affected and analyzed male subjects and female subjects separately, correcting for two tests. Camp et al. (2005) excluded BD relatives and considered dominant and recessive genetic models for three alternative phenotypes (MDD-RE [age at onset before 31] alone, MDD-RE or any anxiety disorder, MDD-RE plus any anxiety disorder), each for four methods of splitting their large multigenerational pedigrees for analysis (limiting genealogical connections to three to six generations). They computed empirical genome-wide lod score thresholds using
regression analyses (Camp and Cannon-Albright, 2005) to estimate the number of independent tests. Male subjects and female subjects were analyzed separately in a secondary analysis. Camp and Cannon-Albright (2005) grouped all anxiety disorders together, regardless of the weight of evidence for genetic relatedness to depressive disorders; however, most of the anxiety diagnoses were categories (panic disorder, agoraphobia, social phobia) that have shown such a relationship (Mineka et al., 1998). Anderson et al. (2008) conducted a genome-wide linkage analysis using 371 microsatellite markers in four families where MDD is co-morbid with unexplained swelling symptoms (USS). They found that of 47 affected individuals, 28 had both MDD and unexplained swelling, 11 had symptoms of swelling alone, and 8 had MDD alone. Parametric marker-specific analysis identified one suggestive locus, D8S260 (LOD = 2.02) and non-parametric multipoint variance component analysis identified a region on 7p (LOD = 2.10). Middeldorp et al. (2009) presented a genome-wide linkage study aiming to find regions on the genome that influence the vulnerability for MDD. Three regions showed suggestive linkage signals. The highest LOD-score of 2.1 was found on chromosome 17 at 52.6 cM along with LOD scores of 1.9 and 1.7 on chromosome 8 at 2.7 cM and chromosome 2 at 90.6 cM, respectively. Verma et al. (2008) reported genome-wide significant linkage on chromosome 15q25.3-26.2 to recurrent early-onset major depressive disorder (MDD-RE). They showed that common variants in NTRK3 or other genes identified in this region might play a role in MDD-RE. However, much larger studies are required for full evaluation of this region.

(Zubenko et al., 2003a) carried out multipoint allele-sharing linkage analyses (LODPAL [(Olson, 1999) (Goddard et al., 2001)]) for five diagnostic models: MDD-RE (onset before age 26); MDD-R; all MDD and BP; “major and minor” mood disorders; and “depressive spectrum” disorders. The linkage study of (Zubenko et al., 2003b) was genome wide. The results in their study were obtained with a model that included one or both of two co-variates: sex of affected pairs and a dichotomized variable which encoded whether or not a family LOD scores at D2S2208 was >0 in (Zubenko et al., 2002a). In a subsequent study, (Zubenko et al., 2002b) presented a more detailed comparison of the
frequencies of each allele of D2S2944 in the same sample of cases and controls. For females, the D2S2944 124-bp allele was significantly more common in cases than controls (odds ratio 4.5, 95% CI 1.9–10.8). These results were supported by evidence from a within-family transmission disequilibrium test of the D2S2944 124-bp allele in another sample of 81 families previously identified through individuals with recurrent early-onset MDD (Zubenko et al., 2001). This finding argues against population stratification as a trivial explanation of the association by linkage disequilibrium. For the same sample of families, Zubenko et al. (2003a) presented evidence of co-segregation of MDD in women with CREBl (located near D2S2208 at 205 cM). Philibert et al. (2003) replicated the association of the 124-bp allele with recurrent early-onset MDD in a comparatively small sample of females (78, 11 affected), although they did not employ some form of transmission disequilibrium testing procedure. Beem et al. (2006) also tested the association of the 124-bp allele of D2S2944 with quantitative measures of anxiety, depression and neuroticism assessed by questionnaires in a Dutch sample of European ancestry. They were not able to confirm the association of the 124-bp allele to depression in females, but they found significant associations with anxiety and anxious depression in males. Recently group of Zubenko have confirmed their earlier results of sex-specific linkage of the CREBl region to mood disorders among women from families with RE-MDD (Maher et al., 2009).

As is the case for all linkage findings in complex disorders, one cannot predict which will prove to be true positives in the long run. Some of the “supportive” findings are sufficiently far apart that they might not be related to the same genetic loci. Two other regions have also produced evidence for linkage to bipolar disorder: chromosome 12q (Green et al., 2005; Shink et al., 2005), which produced strong evidence for linkage in the Utah sample when BD cases were included (Abkevich et al., 2003) but not when they were excluded (Camp and Cannon-Albright, 2005), and chromosome 18q (Fallin et al., 2004). Bipolar findings in both regions are spread over rather wide areas, and it is not known whether there are susceptibility genes common to MDD and BD disorders in these or other regions. But there is sufficient convergence at this point among linkage studies
of MDD and of related personality traits to support optimism about the future of these efforts.

2.9.2 CANDIDATE GENE APPROACH

Most of the published genetic association studies of mood disorders have focused on functional polymorphisms (DNA sequence variations that alter the expression and/or functioning of the gene product) in the loci encoding the serotonin transporter (SLC6A4), serotonin 2A receptor (5HTR2A), tyrosine hydroxylase (TH) (the limiting enzyme for dopamine synthesis), tryptophan hydroxylase 1 (TPH1) (serotonin synthesis), and catechol-o-methyltransferase (COMT) (dopamine catabolism). There are one or more recent meta-analyses of studies of these polymorphisms for MDD, BD, suicidal behavior, and/or for neuroticism.

The CREB1 is a plausible depression candidate gene (Laifenfeld et al., 2005). No association was however, observed between any of CREB1 polymorphisms and childhood or adolescent mood disorders in rather small samples (195 nuclear families and 112 cases vs. control subjects), with both unipolar and bipolar disorders included in the first sample and both MDD and dysthymic disorder in the second sample (Burcescu et al., 2005). Perlis (Perlis et al., 2007) examined six tagging single nucleotide polymorphisms (SNPs) spanning CREB1 and flanking regions for association with a summary measure of frequency and intensity of anger expression. They suggested a strong, gender-specific association between variation at the CREB1 locus and anger expression in MDD. Hettema et al. (2009) examined the evidence for association of the CREB1 to MDD and related phenotypes and concluded that common variations in the CREB1 do not appear to increase susceptibility for MDD or related phenotypes. In a recent study (Maher et al., 2009) studied the functional significance of the CREB1 promoter variant was determined using transfection experiments that employed constructs containing the wild-type or variant CREB1 promoters coupled to a reporter gene. The results support the hypothesis that the A(-656) allele contributes to the
development of MDD in women by selectively altering the activity of the CREBl promoter in glial cells exposed to 17 beta-estradiol.

Most candidate gene studies investigate the association of depression with the 5HTTLPR polymorphism (Peters et al., 2009), and in several studies a significant association was found in case of unipolar major depression (Hoefgen et al., 2005; Jabi et al., 2008) (Kato et al., 2009) and with bipolar depression (Belliver et al., 1998) as well. In other studies this gene was associated with scales measuring neuroticism, such as a scale in NEO-PI-R or the harm avoidance scale in Cloninger’s TCI (Levinson, 2006) a personality dimension thought to be associated with an increased risk for developing depression. Other studies conclude that the role of 5HTTLPR in the background of depression is manifested only in interaction with the effect of life events. Caspi et al. (2003) reported that the relationship between stressful life events and subsequent depression is predicted by the 5HTTLPR genotype. This may suggest that 5HTTLPR plays a role in influencing stress reactivity, rather than depression itself (Levinson, 2006).

Another candidate gene are TPH1 and TPH2, encoding the tryptophan hydroxylase 1 and 2 isoforms respectively which are the synthesizing enzyme of serotonin (Monroe and Reid, 2008; Schosser and Kasper, 2009; Tiwari et al., 2009). TPH1 is located on the human chromosome 11p 15.3-p14, it is about 29kb long and includes 10-11 exons. Two informative SNP’s A218C (rs1800532) and A779C (rs1799913) are both located in intron 7 and are in linkage disequilibrium with each other (Li and He, 2006). Walther and Bader (2003) reported that a tryptophan hydroxylase 2 (TPH2) isoform (rather than TPH1, previously known as TPH) is the predominant form in brain, and Zill et al. (2004a) reported that MDD was associated with 1 of 10 single nucleotide polymorphisms (SNPs) (global empirical p = .0051 for the set of 10 tests) and with 10 SNP haplotypes (global p = .0001) in TPH2 in 300 MDD patients and 265 control subjects. Association of the same SNP was observed in 263 suicide victims versus control subjects (Zill et al., 2004b). Zhang et al. (2005) reported a loss-of-function polymorphism in TPH2, which they found to be associated with MDD (but not BD) in 87 MDD cases versus 219 control subjects, a
small sample size for a complex disorder. However, Zhou et al. (2006) were unable to find this polymorphism in 403 major depression cases and 352 control subjects by direct sequencing or in 1740 depression cases by genotyping. Lee et al. (2009) found a significant association between ‘A’ allele of the TPH1 A218C polymorphism and neural activations in response to negative facial stimuli. Subjects with the A allele of the TPH1 A218C polymorphism showed greater brain activity in the bilateral amygdala under the sad vs. the neutral condition compared with subjects homozygous for the ‘C’ allele.

A more recent hypothesis about depression is that excessive corticotropin activity leads to neuro-toxicity which results in damage to hippocampal cells mediating many depressive symptoms. Genetic factors influence the balance of neuro-toxic and neuro-protective responses to stress. BDNF is one of the neuro-protective proteins and association has been found between reduced levels of BDNF and depression, which has drawn attention to polymorphisms affecting BDNF expression (Levinson, 2006; Chen et al., 2008; Rybakowski, 2008).

2.10 COMMON GENES INVOLVED IN ETIOLOGY OF DEPRESSION AND OBESITY

Mounting evidence from epidemiological studies name genetics as a key component in the co-occurrence of depression and obesity (Kendler et al., 1996; Sullivan et al., 2000). The findings are consistent with a study by Stunkard et al. (2003). These researchers suggest that a genetic predisposition to both depression and obesity may be influenced by unpleasant experiences during childhood (Stunkard et al., 2003). Furthermore, initial results from a study by Dong et al. (2004) found the odds for depression were greatest among persons who were obese (OR = 1.69 for BMI ≥ 30) and whose parents were depressed (OR = 3.06, p < 0.0001), in other words, obesity predicted depression. Conversely, additional results indicated that depression was not a predictor of obesity in this sample (Dong et al., 2004).
Chapter 2: Review of Literature

Genetic factors are believed to play an important role in regulating the development of obesity (Bray, 2006). There has been considerable interest in the neurotransmitter systems, which are hypothesized to regulate behavioral and metabolic responses associated with the development of obesity through feeding and satiety (Barsh and Schwartz, 2002). The interaction of specific genetic alleles with depressive symptoms could be important to understanding gene/environment interactions, since depressive symptoms have been linked with obesity and disregulation in eating (e.g. both hyperphasia and appetite loss) (Stunkard et al., 1990; Faith et al., 2002). Central appetite regulation is believed to take place e.g., in the hypothalamus and the brainstem (Heisler et al., 2003). The hormone ghrelin, produced in the periphery by the stomach as well as centrally in the brain, exerts appetite-increasing effects. Studies have demonstrated that ghrelin inhibits serotonin release (Brunetti et al., 2002) and also that the SSRI, fluoxetine, can reverse this effect (Carlini et al., 2007). Other substances of importance for appetite control are histamine, noradrenaline, leptin, neuropeptide Y and orexin (Stanley et al., 2005). Current models propose that depression and obesity share common pathophysiological elements of the leptin pathway and serotoninergic and dopaminergic neurotransmitter systems (Kalia, 2005; Lopez Leon et al., 2005; Hainer et al., 2006; Kapoor et al., 2009).

2.10.1.1 LEPTIN (OB) AND LEPTIN RECEPTOR (DB)

Leptin (LEP) gene has recently attracted more attention due to its specific effects in the pathogenesis of obesity and depression. Leptin is a hormone mainly produced by adipose tissue. Leptin was initially identified as an anti-obesity hormone, acting as a negative feedback adiposity signal to control energy homeostasis, by interacting with its receptors in the hypothalamus (Elmquist et al., 1998).

The first evidence for a physiological, homeostatic system for body weight regulation was deduced in the 1950s (Kennedy, 1953) and was reinforced after the discovery of recessive mutations, obese (ob) and diabetes (db) (Ingalls et al., 1950) and subsequent parabiosis studies of these strains by Hausberger and Coleman.
(Hausberger, 1959; Coleman and Hummel, 1973), 1959). Their deductions that the ob locus was necessary for the production of a humoral satiety factor and that the db locus encoded a molecule required for response to this factor were confirmed by the cloning of the ob and db genes (Zhang et al., 1994; Tartaglia et al., 1995). For mice, the mutations in the ob gene cause hyperphagia, early-onset morbid obesity, hypothermia, decreased energy expenditure, hyperinsulinemia and infertility due to the hypothalamic hypogonadism. The ob gene product was named leptin (from the Greek leptos, meaning thin), because when injected in animals, it led to reduction in food intake, body weight and body fat in addition to the correction of all the metabolic derangements (Halaas et al., 1995; Pelleymounter et al., 1995).

Leptin is synthesized mainly in white adipose tissue but also in gastric epithelium and the placenta (Campfield et al., 1995; Pelleymounter et al., 1995). The plasma leptin levels correlate strongly with leptin mRNA and the mass of the adipose tissue (Considine and Caro, 1996). The expression of leptin is influenced by several factors, and vice versa, leptin has many stimulatory and inhibitory effects on the neuroendocrine axis in addition to body weight regulation and appetite control (Ahima and Flier, 2000). Its role as the mediator of the adaptation to fasting is manifold. For instance, it serves as an important link between nutrition and the immune system by stimulating inflammatory response and T-cell proliferation (Lord et al., 1998), and it is necessary for the maturation and proper function of the reproductive axis (Chehab, 1996, 1997). Leptin stimulates gonadotropin-releasing hormone (GnRH) (Finn et al., 1998) and corticotrophin releasing hormone (CRH), and a fall in leptin levels suppresses thyroid function by decreasing thyrotropin-releasing hormone (TRH) formation (Legradi et al., 1997). Leptin inhibited glucose-responsive neurons in hypothalamus, and insulin secretion from pancreatic β-cells is decreased through leptin’s effects on ATP-sensitive potassium channels (Harvey et al., 1997) (Spanswick et al., 1997).

Soon after the discovery of leptin, the leptin receptor gene (Ob-R) was isolated in db/db mice (Tartaglia et al., 1995) that have a similar phenotype to ob/ob mice in addition to leptin insensitivity. Ob-R mRNA has multiple splice variants that encode at least six
leptin receptor isoforms (Lee et al., 1996), and only the long isoform (Ob-Rb) contains the intracellular motifs required for signal transduction and transcription activation pathway (Ghilardi et al., 1996).

The short isoforms are expressed in various tissues, e.g. the choroid plexus, vascular endothelium, kidney, liver and gonads (Ahima and Flier, 2000). The long form of the leptin receptor polypeptide is expressed in hypothalamic regions implicated in feeding behavior and energy balance and is co-localized with the neuropeptide mediators of leptin action, such as neuropeptide Y (NPY) and proopiomelanocortin (POMC), agouti-related peptide (AgRP) and cocaine- and amphetamine-regulated transcript (CART) (Baskin et al., 1999; Elmquist et al., 1999). Leptin-sensitive neurons may control feeding by influencing the expression of orexigenic peptides, for instance melanin-concentrating hormone (MCH) and hypocretin. Further, anorexigenic peptides such as POMC and CART are increased in response to leptin administration (Kristensen et al., 1998). Potential transmitters of leptin action in the brain also include corticotropin-releasing hormone (CRH), cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), urocortin, bombesin and serotonin (Flier and Maratos-Flier, 1998).

Fig 2.3: Role of leptin in appetite control. Modified from (Ahima et al., 1996).
2.10.1.2 ROLE OF LEPTIN IN DEPRESSION AND OBESITY

Data available from animal studies have provided evidence that leptin may act as an antidepressant, but evidence for an underlying relationship between depression and leptin insufficiency remains weak (Lu et al., 2006; Lu, 2007). While low levels of leptin have been found to be associated with depressive behaviors both in rodents and humans (Deuschle et al., 1996), information about the role of leptin signaling in human depression is limited and to date controversial. (Deuschle et al., 1996) reported that leptin levels do not differ between depressed patients and healthy controls. Two other studies found higher plasma leptin levels in the depressed patients with a bias in female subjects (Antonijevic et al., 1998; Rubin et al., 2002). In a larger sample size, it has been demonstrated that plasma leptin levels are indeed decreased in patients with major depression independent of their BMI (Kraus et al., 2001; Jow et al., 2006). Decreased levels of leptin in plasma have also been observed in patients with bipolar disorder (Atmaca et al., 2002). (Comings et al., 1996) were the first to suggest that genetic variants in the vicinity of LEP gene may be causally involved not only in human obesity but also associated with behavioral disorders. In the light of leptin's ability to reduce depressive behavior in animal models, it is possible that “leptin resistance” may contribute to the higher rate of depression in obese subjects (Lu, 2007). This hypothesis helps in interpreting some of the conflicting results obtained in relation to circulating leptin levels in depressed patients. Altered leptin levels can also be the result of functionally defective leptin protein or altered expression caused by variations in the LEP gene promoter (Oksanen et al., 1997).

2.10.2.1 SEROTONIN IN WEIGHT REGULATION, EATING DISORDERS AND DEPRESSION

Serotonin has been shown to modify normal aspects of behavior, such as food intake, sexual activity and aggression, and seems also to be involved in the regulation of respiration, sleep, cardiovascular function, body temperature, pain perception, gastrointestinal function and hormonal release (Lucki, 1998). However, although
serotonin influences all these functions, its presence does not seem to be a prerequisite for any of them. Animals from which serotonin has been depleted hence survive, and do not display any gross abnormalities (Eriksson and Humble, 1990).

When a new drug, iproniazid, was assessed as a putative treatment for tuberculosis in the late 1950s, it was discovered that some of the patients displayed a marked elevation of mood (Loomer et al., 1957). Almost at the same time, another compound, imipramine, was also demonstrated to exert an unexpected antidepressant effect (Kuhn, 1958). Whereas iproniazid was subsequently shown to be an MAO inhibitor (MAO-I), imipramine was shown, by Axelrod and co-workers, to be a noradrenaline reuptake inhibitor, and later, by Carlsson and co-workers, to inhibit the reuptake of serotonin also, the later finding paving the way for subsequent introduction of the selective serotonin reuptake inhibitors (SSRIs) as treatment for depression (Carlsson et al., 1968; Eriksson and Humble, 1990).

The discovery that serotonin depletion by parachlorophenylalanine (pCPA), a TPH inhibitor, could reverse the antidepressant effect of reuptake inhibitors or MAO-Is (Shopsin et al., 1975) lent support to the notion that the antidepressant effect is, at least partly, mediated by serotonin. This was also supported by numerous subsequent studies showing that acute tryptophan depletion (ATD) can trigger the onset of depressive symptoms in patients in remission as well as lower mood in healthy subjects with a family history of depression (Bell et al., 2005).

Drugs that modulate the output from serotonergic synapses are effective not only for the treatment of depression, but also for the treatment of several other psychiatric disorders, such as premenstrual dysphoria (PMD), panic disorder, general anxiety disorder (GAD), posttraumatic stress disorder (PTSD), social phobia, obsessive compulsive disorder (OCD) and bulimia nervosa (Eriksson and Humble, 1990). Notably, with respect to some of these conditions, such as PMD (Landen and Thase, 2006) and panic disorder (Eriksson and Humble, 1990) the effects of SSRIs in terms of effect size and response rate are considerably higher than in depression. Further supporting the hypothesis that serotonin
influences other aspects of behavior than mood. ATD has been reported to induce an increase in food intake in bulimic patients (Kaye et al., 2000) and an increase in irritability in women with premenstrual dysphoria (Menkes et al., 1994; Bond et al., 2001). With respect to anxiety disorders, ATD alone does not trigger anxiety or anxiety attacks, but enhances the response to an anxiety-provoking challenge, e.g., CO2 exposure (Anderson and Mortimore, 1999).

Appetite, food intake and satiety are regulated by an intricate network, which involves both peripheral and central mechanisms, and in which serotonin plays an important role. Agents enhancing serotonergic transmission induce a decrease in food intake in both animals and humans (Noach, 1994; Sargent et al., 1997), and drugs inhibiting serotonergic transmission may exert the opposite effect (Kluge et al., 2007) (Nasrallah, 2008). The influence of serotonin on satiety and food intake is believed to be mediated mainly by two serotonin receptors – 5-HT1B and 5-HT2C. Whereas stimulation of 5-HT1B causes a decrease in meal size and total food intake, activation of 5-HT2C leads to a decrease in intake speed (Simansky, 1996).

2.10.2.2 INTERACTIONS BETWEEN SEROTONIN RELATED GENES, DEPRESSION AND OBESITY

Because of the involvement of serotonin in appetite regulation as well as in other traits commonly occurring in patients with eating disorders, such as anxiety, depression and poor impulse control, association studies in this field have to a great extent been focused on serotonin-related genes, e.g., HTR2A (Collier et al., 1997; Campbell et al., 1998; Sorbi et al., 1998; Naemics et al., 1999; Ziegler and Gorg, 1999; Gorwood et al., 2002), HTR1D (Bergen et al., 2003; Brown et al., 2007), TPH1 (Monteleone et al., 2007) and SLC6A4 (Sundaramurthy et al., 2000; Fumeron et al., 2001; Lauzurica et al., 2003; Matsushita et al., 2004; Frieling, 2006).

Recent studies of Argentinean adolescents (Sookoian et al., 2007) and young adult males (Sookoian et al., 2008) found significant associations between a polymorphism of the
serotonin transporter \textit{SLC6A4} and being overweight (Sookoian \textit{et al.}, 2007). In a US sample of young adults, this gene was also found to be associated with obesity, primarily among men (Fuemmeler \textit{et al.}, 2008). In addition to \textit{SLC6A4}, the gene that encodes monoamine oxidase A (MAO-A)—an enzyme that metabolizes brain amines including serotonin and dopamine has been examined as a predictor of obesity. In a large UK cohort \((n = 1,150)\) of Caucasian females, significant associations were detected between MAOA and BMI, with the low-activity u-VNTR genotype \((3/3)\) being more frequent among obese females (Need \textit{et al.}, 2006). This finding supports a previous family-based study in which preferential transmission of the low activity allele was observed among subjects with BMI \(>35\ \text{kg/m}^2\) (Camarena \textit{et al.}, 2004). Association between the low activity allele and obesity was also observed among white and Hispanic, but not African-American, men in a US cohort of young adolescents and adults (Fuemmeler \textit{et al.}, 2008). (Fuemmeler \textit{et al.} (2009) used multiple logistic regression to investigate interactions between candidate genes and depression on risk of obesity (BMI>30) or overweight + obese combined (BMI >25). Males with an MAOA active allele with high depressive symptoms were found to be at decreased risk of obesity and overweight + obesity.

2.10.3 ROLE OF CHROMOSOME 2 IN DEPRESSION AND OBESITY

Chromosome 2 \((2q34-q37)\) has been found to be linked with obesity (Damcott \textit{et al.}, 2003). Li \textit{et al.} (2007), studied obese subjects and found significant linkage on the 2q34 region for total cholesterol and suggestive linkage on the marker D2S2944 \((210.4\ \text{cM})\). (Iwasaki \textit{et al.}, 2003), based on whole genome scans found linkage between D2S2944 marker \((\text{LOD} = 1.45)\) and type 2 diabetes and BMI in Japanese families. At the same time linkage and association of the D2S2944 tetranucleotide repeat region with major depression has been reported by group of Zubenko (Zubenko \textit{et al.}, 2002a; Zubenko \textit{et al.}, 2002b; Zubenko \textit{et al.}, 2002c). Using logistic regression to analyze adjusted and interactive D2S2944 associations with depression, controlling for all other risk factors. Langbehn \textit{et al.} (2006) reported a strong association with DSM-IV major depression and the 124 bp allele, specifically in those with history of alcohol abuse/dependence and/or
antisocial personality disorder (ASPD). Beem et al. (2006) tested for association of 124 bp allele to continuous measures of anxiety, depression and neuroticism and found significant associations with anxiety and anxious depression in males only. Zubenko et al. (2009) confirmed the results of linkage with CREBI and major depression using a simulation approach to estimate the empirical significance of their previous results. These findings suggest that this region of chromosome 2 is linked to depression as well as metabolic disorders like obesity.

2.11 SOCIOECONOMIC (SES) STATUS, DEPRESSION AND OBESITY

Besides biological and genetic factors, social factors also contribute to depression. Goodman et al. (2003) reported that socioeconomic status is an important risk factor for depression. In above-mentioned study the impact of lower household income was approximately two fold higher for students attending poor versus rich schools. Although there is a lack of consensus on the exact nature of the relationship between depression and obesity, researchers agree that low socioeconomic (SES) status is a risk factors in the development of both depression and obesity. The rates of depression range from 12% to 36% among women on welfare (Lennon, 2001). Chronic illness or disability and involvement in an abusive or violent relationship (common findings among welfare recipients) significantly increase the risk for depression among welfare recipients (Lennon, 2001). Findings from the only longitudinal study conducted to assess the impact of welfare on psychological health, indicated that mood disorders, such as depression, are a risk factor for and outcome of receiving welfare (Danziger, 2000). Furthermore, depression and the associated sequelae interfere with the ability of women to leave welfare for work (Siefert et al., 2000).

There are increased societal concerns that obesity carries with it a higher risk for psychosocial difficulties for individuals of all ages (Pyle, 2006; Shoup et al., 2008). However, studies correlating these psychosocial factors such as depression (Simmons-Alling, 2008), body dissatisfaction (body image), self-esteem (Latner et al., 2005;
Wardle and Cooke, 2005) and weight-based teasing, (Goldfield et al., 2007) are at best inconclusive as they relate to obesity (Alleyne and La Point, 2004; Swallen et al., 2005; Wardle and Cooke, 2005; Goldfield et al., 2007; Janicke et al., 2007; Mauro et al., 2008; O'Dea, 2008). This is especially true in the younger populations (Carpenter et al., 2000; Alleyne and La Point, 2004; Swallen et al., 2005; Goldfield et al., 2007; O'Dea, 2008).

It appears that direct causal relationships between SES, obesity, and psychosocial factors are as complex as the disease itself. Much of the complexity surrounding the relationship between obesity and psychosocial factors is related to inconsistent study designs, variance in the demographics of subjects studied, and socio-cultural surroundings of the subjects (Alleyne and La Point, 2004; Latner et al., 2005; Wardle and Cooke, 2005; Janicke et al., 2007; O'Dea, 2008). The psychosocial complexity is further clouded by pre-existing psychosocial pathology which may or may not impact the degree of psychosocial symptoms reported by obese/overweight subjects to clinicians and/or researchers (Swallen et al., 2005; Wardle and Cooke, 2005; Mauro et al., 2008; Simmons-Alling, 2008). In general, obese individuals are not consumed by psychosocial factors relating to their condition anymore than their normal weight or underweight counterparts (Wardle and Cooke, 2005; O'Dea, 2008).

2.12 GAPS IN EXISTING RESEARCH

Depression is unique in that dysfunction of the master control organ, brain, leads to challenges often seen by the clinician in his general practice, namely disorders like hypertension, obesity and/or diabetes, social withdrawal etc. Given the psychobiologic complexity of depressive disorders, it is not surprising that the recognition of specific genetic influences combined with environmental interplay may assist in early recognition of various etiologies of depressive disorders and help in appropriate therapeutic measures. Future research will take advantage of the completion of the sequencing of the human and mouse genome coinciding with the revolution in bioinformatics. Integration of these emerging technologies for genetic analysis will provide the basis for gene
identification and functional studies in depression. Current treatments are limited by lack of knowledge of biology of mood disorders.

Fig 2.4: Several factors involved in pathogenesis of complex disorder like depression

In modern times several research approaches suggest that personality and the liability to psychiatric illnesses like depression is influenced by many genes. If it is true it could shed light on genetic architecture of psychiatric illnesses. More over the genetic profile of different populations for the depressive disorders will serve as platform to diagnose the risk individuals from the high-risk families at early age and design strategies for early and timely intervention of the disease will be possible. Obesity is also one of the major disorders worldwide and this study will also focus on its relation with depression. India is developing country and most of its population is in the lower income group. This study
will try to find out whether the socioeconomic status plays any part in the development and severity of depressive symptoms.

Genetic studies may help us better understand the biological causes of mood disorders. Present study has been undertaken with an aim to investigate the role of variations in *LEP* and *TPHI* gene in susceptibility for depression and obesity under influence of socio-demographic and environmental factors.