



Structural and Neurochemical Alterations in Brain Regions of Depression and Suicide Patients

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Abstract

Depression is a mental disorder that makes an individual responsive to negative stimuli as higher cognitive functions of the brain of the individual like perception, attention, memory related functions, planning, decision making etc. are seriously challenged by the causes like excessive stresses in life, serious illness, loss of self-esteem, certain medications etc. Erroneous information processing in the brain of depressive individuals attaches them to the feelings of loss, sadness and hopelessness. In extremely stressful situation the cognitive functions of the depressive individuals may be impaired to such an extent that they may have the feeling of entrapment for which they can take the way of suicidal acts for escape. A number of brain regions that are involved in higher cognitive functions are altered in depression patients, suicidal individuals and in complete suicides. Along with the morphological changes, monoaminergic neurotransmission system is also severely deteriorated in these brain regions indicating their possible involvements in regulating cognitive activities. Monoaminergic dysfunctions may give rise to serious cognitive impairments and deterioration of associated mental functions required for maintaining normal internal homeostasis. Loss of cognitive functions makes an individual incapable to interact properly to various aspects of normal life functions making them depressive and severe depression may be the forerunner of suicidal acts.

Keywords: Major depression disorder; Suicide; Prefrontal cortex; Norepinephrin; Serotonin; Dopamine; Raphe nuclei; Locus ceruleus

Introduction

Depression is a common mental disorder that accompanies sadness, loss of interest or pleasure, guilty feelings, disturbances in sleep and many cognitive deficiencies that impair an individual's ability to function properly in daily works deteriorating the quality of his life. At least 350 million people in the world at present are the victims of depression making it as a leading cause of disability globally [1]. Onset of depression may be triggered by multiple factors like genetics, changes in hormone levels, certain medical conditions, stress, grief or difficult life circumstances etc. Any of these factors alone or in combination can give rise to changes in brain chemistry that give rise to many symptoms of depression [2]. Depression is considered as the psychiatric diagnosis most commonly associated with suicide [3]. It has been reported that more than two-thirds of suicide completers and suicide attempters, exhibit serious depressive episodes at the time of their suicidal acts [4]. Recent studies have demonstrated that structural abnormalities occur in brain regions implicated in higher cognitive functions both in depression patients and in suicidal brains [5-7]. Furthermore, neurocircuits involving monoaminergic neurotransmission in brain regions associated with higher cognitive functions are also severely altered both in depressives and suicidal patients [8-12]. Possibly both these alterations make individuals deprived of higher cognitive abilities that precipitate the symptoms of depression in them and suicide may occur when the situation worsens.

Depression is a Major cause of Suicide

Depression is a state of mental disorder in which person's mood is severely impaired by the feeling of loss, sadness, hopelessness, failure etc. In extremely depressed individuals cognitive functions like attention, concentration, various forms of memory, information processing, executive functions are declined resulting in many forms of disabilities that lead to the deterioration of the quality of life [13] and suicide is of usual occurrence when the cognitive functions worsen [14]. Depression is regarded as a major psychiatric disorder associated with suicide [15-18]. It has been reported that 70-90% of the suicidal victims were accompanied with some mental disorder when they were alive of whom 60-70% were suffering from depression [19]. Depression can be triggered by one or many factors like- stressful life situation, serious illness, loss of self-esteem and identity, heredity, uses of certain medications etc. [20-22]. Depressive disorders can be broadly classified into a major depressive disorder (MDD) or unipolar disorder, bipolar disorder and persistent depressive disorder (PDD) [23,24]. The term unipolar refers to one extreme mood i.e. depressed mood. In contrast bipolar depression has two poles of mood i.e. an individual sometimes experiences depression and elevated mood or mania at other times. In MDD many symptoms like depressed mood, loss of pleasure or interest, lack of ability to concentrate, remembering and decision making, reduced energy etc. last at least for two weeks. In bipolar disorder same symptoms of MDD alternate with manic phase in which an individual experiences abnormal happiness or irritations that may last for a week. Both the symptoms of MDD and bipolar disorders produce serious problems in maintaining normal functions of life [25]. Bipolar disorder is further classified into Bipolar I and Bipolar II in which individuals with the former disorder experience full mania and depression, while the individuals of the later group experience

hypomania which is less severe with regard to functional impairment in addition to depression [26-28]. PDD, formerly called dysthymia, is a chronic form of depression that is less severe than MDD and lasts for at least 2 years [28]. Several criterion of MDD like helplessness, hopefulness, burdensomeness to loved ones make the individuals isolated and motivate them for suicidal acts [29,30]. Clinical features of depression increases suicidal ideation and suicidal behaviour and the severity of depression is directly related with suicidal acts [29,31-33]. It has been reported that suicidal patients are overwhelmed with the feeling of entrapment [29-34]. Perhaps the feeling of entrapment by intolerable internal and external stresses acts as the driving force for suicidal behaviour and suicidal acts as the depression patients consider it as the strategy for escape for ever [35,36].

Structural Changes in Brain Regions may Contribute to Cognition Deficiencies in Depression and Suicidal Patients

Cognition can be defined as a mental process by which external and internal information are transferred into signals that the brain can understand, reduced to into a critical concept, and elaborated if needed, stored and recovered. These are higher-level functions of the brain that encompass perception, attention, coding, retention and recall of memory, decision making, reasoning, problem solving, planning and executive actions [37]. Depressive disorders are reported to be associated with variety of cognitive deficits that include attention, learning, memory processing and executive functions [13,38,39]. In normal individuals attention is generally biased towards the positive stimuli. In contrast individuals with depressive disorders show attention bias towards negative stimuli. Their incapability to detach themselves from negative stimuli indicates erroneous information processing so that attention moves away from positive towards the negative stimuli [13]. A number of brain regions responsible for higher cognitive functions are altered in depression patients. Prefrontal cortex (PFC) which is associated with higher cognitive functions like encoding memory, intelligence, language, planning, decision making [40,41] are altered in the patients of depression. For example dorsolateral PFC that responds to working memory task remains hypoactive in depression [42]. Moreover, MDD patients exhibited a cortical thinning of the middle frontal cortex (MFC) the brain region needed for maintaining the normal social behaviour [5,43]. In addition, MDD patients have shown reduced gray matter volume in the regions of the prefrontal circuits that included dorsolateral and dorsomedial prefrontal cortices, lateral and medial orbitofrontal cortices [44]. It has been shown that total gray matter volume is inversely correlated with depression severity and suicide attempts and suicide attempters showed reduced gray matter volume in several brain regions including prefrontal cortex. Possibly reduction of gray matter in critical cortical areas in suicidal patients cause serious cognitive deprivation in them for performing planned goal-directed behaviour. Coupling this inability with depressive symptoms they feel more helplessness to attempt suicide [45]. Amygdala (Ag) is a part of the neural circuitry involved in emotion but also plays an important role in learning the emotional component of experiences [46,47]. It has been suggested that frontal cortex modulates the amygdalar activities and mediates cognitive emotion regulation [48]. Z10C. In MDD patients, elevated activity of the Ag has been reported which is found to be associated with the hypoactivation of dorsolateral prefrontal cortex (DLPFC). This increased activity of Ag is supposed to arise from the hypoactivity of DLPFC which makes it less efficient in exerting regulatory influence over Ag [49]. Hippocampus (H) is a brain region

which is very important for learning, memory acquisition, motivation and emotion [50]. H is connected to diverse brain regions like-PFC, thalamus, Ag, basal ganglia and hypothalamus which in union makes a neuronal network for mood regulation [6]. Thus it seems probable that any structural abnormality in H will be reflected in the cognitive activity of an individual. In fact, hippocampal volume has been found to be significantly reduced in patients with the episodes of major depression [6,7]. Basal ganglion is another part of the brain that is composed of a group of subcortical nuclei primarily involved in motor control in individuals. Motor functions of the basal ganglia are mediated mainly by the motor areas of the frontal cortex [51]. Basal ganglia are associated with the cerebral cortex by five parallel segregated circuits. Of these, two circuits are associated with the motor areas of the cortex. However, three other circuits are connected to non-motor areas of the frontal cortex known to be associated with planning, learning, attention, working memory and many other aspects of higher cognitive functions [52]. Thus it seems probable that damages or alterations in basal ganglia will also impart negative influences on cognitive functions of individuals and contribute to appear the depressive symptoms in them. In fact, basal ganglia have been documented as a site for structural changes in major depression. Magnetic resonance imaging studies revealed that depressed patients possessed significantly reduced caudate nucleus and putamen than the control subjects [53,54]. Furthermore, damages in the basal ganglia exhibit same cognitive deficits that can be brought about by damaging the frontal cortex. It indicates basal ganglia participate in circuits with the cognitive areas of the cerebral cortex [53]. Thus it is probable that combined structural abnormalities of frontal cortex and basal ganglia may impart profound cognitive and motor deficits making an individual depressed and functionally disable. One of the major causes of the reduction of brain volume is probably the glutamatergic neurotransmission. Glutamatergic synapses are found throughout the brain and it has been proposed that abnormal glutamatergic neurotransmission possibly contribute to impaired synaptic and neuronal plasticity observed in severe and recurrent mood disorders [55]. In chronic stress excessive glutamatergic transmission may lead to excessive activation of the N-methyl-D-aspartate receptor (NMDA) type of glutamate receptor [56]. Indeed, in a post-mortem study of MDD and bipolar disorder subjects, high glutamate level glutamate was observed in frontal cortex [57]. It is possible that excessive cortical glutamatergic transmission lead to NMDA receptor mediated Ca^{+2} influx in the postsynaptic neurons causing the cytotoxicity, neuronal atrophy and their ultimate loss leading to structural deterioration of brain structures related to cognitive functions precipitating the symptoms of depression [56].

Cognitive Deficiencies are Associated with Dysfunctions of Monoamine Neurotransmitter System Observed both in Depression Patients and in Suicide Brains

Normal cognitive behaviours in individuals require proper regulation of neurotransmitter release and keeping normal levels of neurotransmitters in the brain [58]. It has been proposed that depression arises due to the deficiencies of monoaminergic neurotransmitters like norepinephrin (NE), serotonin (5-HT) and dopamine (DA) in the brain synapses. In contrast, mania which is one of the symptoms of bipolar disorder is accompanied with monoamine excess in brain [59].

Early researches which made the foundation of the hypothesis advocating the essentiality of the monoaminergic neurotransmission in preserving normal mood is the outcome of some important clinical and experimental observations. For example, it was found that reserpine, used as the antihypertensive drug in human, caused the depression in its users and destroyed the monoamine stores in rat brain. It indicates that the depression may arise due to the lack of monoamine neurotransmission [60]. It is important to mention here that once a neurotransmitter has carried out its required function after being released into the synaptic cleft, it needs to be cleared off from the synapse to prevent undesired over-stimulation of the postsynaptic neuron. In one mechanism of clearance, monoamine neurotransmitters can be transported back into the presynaptic neuron from which they are released and are broken down by the enzyme monoamine oxidase to become inactivated. They may also be returned into the presynaptic neuronal vesicles through the transporters on their surfaces for storage for future release [61]. As reserpine blocks the vesicular monoamine transporter monoamines cannot be transported back to the presynaptic vesicles for storage and undergo enzymatic degradation in the presynaptic cell [62]. As the depleted transmitters are not replenished quickly, the overall result is that, patients using this drug remain deficient in monoamine neurotransmission due to their depleted presynaptic vesicular transmitter store and develop the symptoms of depression. Another drug iproniazid which was used for the treatment of tuberculosis acted as mood enhancer by inhibiting monoamine oxidase that prevented monoamine neurotransmitter degradation. Furthermore, imipramine, an antipsychotic drug blocked the monoamine reuptake into the presynaptic neuron allowing prolonged neurotransmitter activities in the synapse and promoted antidepressant effects [60]. 3-methoxy-4-hydroxyphenyl glycol (MHPG), a metabolite of NE degradation is present in the urine of which 20-30% is brain derived [60]. This metabolite was reported to be decreased significantly in patients with depression compared to control subjects. It has been seen that depressed patients under imipramine therapy excreted greater quantity of MHPG along with mood elevation compared to lesser excretion of this NE metabolite before the start of their therapy [63]. This finding indicates that imipramine by blocking NE reuptake from the synapse increased neurotransmitter activities to rescue the patients from depression. Thus it appears that NE is an essential neurotransmitter for maintaining normal mood in individuals. The cell bodies of the NE secreting cells lie in the locus ceruleus (LC) of the pons and project mainly to the frontal cortex. NE neurons also project to the limbic system whose various components like Ag, H and hypothalamus are implicated in emotion and cognition [64]. LC also densely innervates other monoaminergic nuclei including serotonergic raphe nuclei (RN) and dopaminergic ventral tegmental area (VTA). This widespread innervation of brain areas of LC indicates that noradrenergic transmission globally modulates brain functions [65]. In human, PFC which is responsible for higher cognitive functions like planning, organization, attention, memory formation and retrieval, decision making are reported to be modified by NE [66]. Pharmacological activation of prefrontal NE α 2-adrenoceptors by agonists in experimental primates and rodents has shown to improve memory and attention [67-69]. In contrast blocking α 2-adrenoceptors by its antagonists inhibit prefrontal cortex mediated working memory performances in monkeys [70]. It has already been discussed that hypo-activation and gray matter volume reduction of frontal cortex occurs in depression MDD patients who are cognitive deficient. Most possibly, loss of frontal cortical region destroyed the synapses contributed by NE neuron preventing the NE neurotransmission to occur and subsequently led to the deficiencies of higher order cognitive

functions. Many findings demonstrate that cognitive deficits such as poor concentration, impaired memory, inappropriate choice are linked to suicide and the subjects who had attempted suicide earlier demonstrate deficits in problem solving, decision making and verbal fluency [71-73]. Furthermore, depressed suicide attempters and victims have performed worse than psychiatrically normal individuals with respect to intelligence and executive functions [74]. Thus it appears that poor cognitive functions predispose suicidal behaviours. Since NE plays an important role in modulating cognition, it is probable that NE transmission inhibition due to structural deterioration in frontal cortical and other brain region may be an important factor for cognitive deficiencies leading to depression and suicidal acts [75].

Serotonin (5-HT) is a monoamine neurotransmitter known to involve in mood regulation [60]. Serotonin is unable to cross the blood-brain barrier but its metabolite 5-hydroxyindoleacetic acid (5-HIAA) is actively transported out of the brain that can be measured in cerebrospinal fluid (CSF) and urine. Production of 5-HT in brain can be measured by estimating 5-HIAA in CSF and urine [76]. Many studies have revealed the reduced level of CSF 5-HIAA in depressed patients [77,78]. Furthermore, it has been reported that reduced serotonergic activity indicated by lower CSF 5-HIAA was associated with a history of planned suicide attempt and with suicide attempts that resulted in greater medical damage [79,80]. 5-HT is synthesized in neurons whose cell bodies lay in the midbrain raphe nucleus (RN) and project to frontal cortex, basal ganglia, H and hypothalamus etc. [81]. Serotonergic system dysfunction has been implicated in aggression, eating and personality disorders, vulnerability to alcohol misuse. Apart from these, this system also regulates sleep, appetite circadian rhythm and cognition that control the mood of individuals and all the functions are often disrupted in the episodes of major depression [24]. By using transcranial ultrasound technique (TCS) a number of studies have shown that echogenicity of the RN of the brain stem significantly reduced in MDD patients and patients with suicidal ideation [82-84]. The etiology of decreased echogenicity of RN is thought due to the changes in tissue cell density, alteration of interstitial matrix components or changes of fibre tracts etc. In other words, decreased echogenicity of RN indicates some sort of lesions in RN. It has been considered that these changes in RN reflect the decreased level of 5-HT output of the RN neurons to their targets that bring about the clinical features of depression and suicidal ideation due to the disruption of cognitive function as well as mood [83,84]. Another important feature of RN reflects diminished 5HT transmission in its targets. In RN 5-HT_{1A} receptor acts as an inhibitory auto receptor on the surface of 5-HT neurons [85]. 5-HT_{1A} auto receptors are negatively coupled to G-protein causing the inhibition of adenylyl cyclase and inhibit 5-HT neuronal activities. Furthermore, these auto-receptors activate K⁺ channels on neuronal surface to efflux K⁺ ions causing the hyper-polarization of the cells inhibiting their firing ability [86]. Locally released 5-HT can act on the auto receptors of RN 5-HT neurons that inhibit further release of 5-HT on the targets [87]. It has been found, in post-mortem midbrain sample of suicidal victims with major depression, that 5-HT_{1A} auto receptor levels are elevated. Possibly increased auto inhibition in the raphe nuclear 5-HT neurons causes reduced serotonin release in PFC that relate to symptoms of depression and suicide [11]. It has been reported by many studies that postsynaptic 5-HT receptor density is increased in PFC as well as in H of suicide victims [10,12,88,]. The possible explanation of such increase in postsynaptic receptors is that it is a phenomenon of compensatory receptor up-regulation in response to reduced presynaptic serotonin

release [89]. In serotonergic synapses of PFC, presynaptic 5-HT transporter (SERT) regulates the intra-synaptic 5-HT level by the reuptake of 5-HT into the presynaptic neuron. It is interesting to note that reduced expression of presynaptic SERT in PFC of suicidal victims with major depression has been reported by some studies [90,91] which can be designated as a compensatory down regulatory mechanism in response to deficient 5-HT neuro-transmission [87]. Thus raphe nuclear decreased serotonergic density coupled with altered pattern of distribution of 5-HT_{1A} receptors as well as postsynaptic 5HT receptors and presynaptic SERT in the cortical synapses may account for inhibited serotonergic neurotransmission at its targets especially in PFC may give rise to the symptoms of serious mood disorder in major depression and possibly provoke suicidal acts.

It has been suggested that under-activity of forebrain DA impairs the activities in critical brain cortical regions that are manifested in clinical symptoms of depression [92]. Homovanillic acid (HVA), a metabolite of DA that can reach from brain to the CSF easily and to urine partly, is used to associate the DA level in brain. In fact there are instances which show that HVA levels are decreased in CSF and urine in depressives and suicides attempters with depression [93-95]. Furthermore, it has been seen that urinary HVA of patients with depression who reattempted suicide had significantly lower urinary HVA than those who did not reattempted suicide [93]. In addition, agents that enhance DA transmission exert antidepressant effects in human. For example, antidepressants nomifensine and amineptine act as DA reuptake inhibitors in synapses and allow prolonged dopaminergic neurotransmission in the synapses [96,97]. It has been seen that psycho stimulant amphetamine, that enhances mesolimbic dopaminergic activity, when withdrawn from its users they experience depression that can be relieved by amineptine [97]. Thus it seems probable that mesolimbic DA deficiency is linked to depression. Our brain has a 'reward circuit' that denotes the mesolimbic system comprising ventral tegmental area (VTA) of midbrain, sends DA secreting neurons to nucleus accumbens (NAc), Ag, H, PFC etc. In response to natural stimuli like, food, sex etc. DA is released from VTA into its targets which is important for reward related learning and motor actions needed for achieving the rewards [98]. Since the reward seeking behaviour in individuals has an emotional basis and since it is a type of learned behaviour, it can be speculated that deprivation of VTA DA in brain regions may induce emotional and cognitive problems that may lead to depression. In this context it is important to mention that animal models of depression have demonstrated the association of mesolimbic DA system dysfunction and certain antidepressants have enhanced mesolimbic dopaminergic transmission [99]. It has been observed that repeated treatment of rat with antidepressant drugs enhanced loco-motor hyperactivity induced by DA agonists when injected directly into NAc, the brain region which is a vital component of mesolimbic reward circuit [99-103]. These instances emphasize the mesolimbic dopaminergic association with depression. As DA induces reward related synaptic plasticity in the brain regions belonging to the reward circuit [98]. It seems probable that mesolimbic DA deficiency may distort synergistic activities of the reward circuit making an individual reclusive to acts in response to natural rewards for survival that severely alter the internal homeostasis of an individual and this may contribute to depression and suicidal acts.

Discussion

Depression is a common psychiatric illness that causes serious disability and mortality throughout the world [39]. Depressive individuals suffer from various cognitive deficiencies. Indeed, many brain regions involved in higher cognitive functions undergo structural alterations in these individuals. These altered brain regions which are the home of activities of some monoaminergic neurotransmitters implicated in higher cognitive functions and mood development also become deficient of these neurochemicals. Thus the combined effect of structural and neurochemical dysfunctions may have tremendous negative impacts on physical as well as psychological aspects of an individual that may precede the clinical features of depression. Suicidal ideation seems to be a fruit of severe depression as clinical and epidemiological studies have demonstrated a strong correlation between major depression and suicidal behaviours [33]. Luckily, a number of manageable drugs are available for treating MDD and patients obtain significant benefits within 4-6 months after the initiation of treatments. Among these drugs, tricyclic antidepressants, monoamine oxidase inhibitors, selective 5-HT reuptake inhibitor etc. are most important [100]. However, timely onset of treatment may only prevent the devastating consequence of this disease at the extreme of which is complete suicide.

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