1. INTRODUCTION
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Depression is a mood disorder characterized by a broad range of symptoms including altered mood or cognitive functions and recurrent thoughts of death or suicide (Victor, 2005), if left untreated may affects the quality of life for years. Depression is not only detrimental to the individuals it affects but it is also a costly disorder to the society. World Health Organization (WHO) predicts that depression will become the second leading cause of premature death or disability worldwide by the year 2020 (WHO, 1999).

Traditional pharmacotherapy for depression has been discussed primarily in terms of effects on noradrenergic and serotonergic systems. The inability of these traditional antidepressant agents to provide an adequate explanation for the shortcomings such as low remission/high treatment-resistance rates, treatment failures, slow onset of action, side effects (Zajecka, 2000) such as weight gain, sexual dysfunction, insomnia, toxicity in overdose and drug-drug interactions, has led to the need to develop dopamine based monoaminergic hypothesis. Ranrup and co-workers presented the first evidence for a dopaminergic dysfunction in depression (Ranrup et al., 1975). These evidences then prompted the multiple lines of investigations on the possible role of dopamine and dopaminergic dysfunction both in the pathogenesis of depression and in the mechanism of action of antidepressant treatment.

Despite growing evidences for the role of dopamine and dopaminergic dysfunction in the pathogenesis of depression, little knowledge is available about the specific role of dopamine in the pathophysiology of depression. Such large body of evidences from animal and clinical studies have suggested that sensitization of D2-like dopamine receptors in the mesolimbic dopamine system may represent a 'final common pathway' in antidepressant action (Corrigan et al., 2000; Maj et al., 1997; Muscat et al., 1992; Papp et al., 1993; Willner et al., 2005). However, poor availability of effective
dopaminergic agents as antidepressants at clinical use in depression and diversity as well as heterogeneity within such dopamine receptors etc. has further imposed to explore of its role in depression (Memo, 1990).

Likewise, various experimental and clinical studies indicate a possible link between cholesterol and depression. Cholesterol, an essential constituent of human brain plays significant role in synapse (Goritz et al., 2005) and myelin formation (Snipes and Suter, 1997), membrane organization, dynamics (Pucadyil and Chattopadhyay, 2006) and various biological functions ranging from membrane trafficking to signal transduction (Maxfield and Tabas, 2005). The sufficient availability of cholesterol is necessary for normal neuronal function; and both lack as well as surplus of cholesterol impairs these features (Matthias and Stefano, 2012).

Depletion of brain cholesterol leads to synaptic degeneration, deranged neurotransmission and decreased synaptic plasticity (Koudinov and Koudinova, 2005). Further, brain cholesterol is primarily derived by de novo synthesis. It has been shown that increased transfer of circulating plasma cholesterol to the brain may be related to the onset of neurodegeneration (Dietschy and Turley, 2001). Likewise, it has been proposed that depression may be associated with the alteration in serum lipid levels and such alterations may become a marker for major depression and suicidal behavior in depressed patients (Park et al. 2014; Kale et al. 2014; Nakao and Yano, 2004; Maes et al., 1997). In fact, hypercholesterolemia is suggested to partly mediate the age related brain changes (Yehuda et al., 2002).

Hypercholesterolemia may decrease the fluidity of cell membranes and membrane permeability (Barenholz, 2002) with changes in second messenger system and in neurotransmission (Ohvo-Rekilä et al., 2002). This may be reported to be associated with poor treatment outcome with different classes of antidepressants such as selective serotonin reuptake inhibitors (SSRI) (Sonawalla et al., 2002; Papakostas et al.,
and nortryptiline (Papakostas et al., 2003) in major depressive disorder (MDD). It has been proposed entity of ‘vascular depression’ for hypercholesterolemia as a risk factor in the pathophysiology of depression (Iosifescu et al., 2005). Thus, lowering of cholesterol levels with cholesterol-lowering drugs may improve the effectiveness of antidepressants agents and clinical outcomes in depression (Young-Xu et al., 2003).

Thus cholesterol-lowering drugs, which block systemic cholesterol synthesis, may be a potential treatment option for a range of neurological disorders (Cucchiara and Kasner, 2001; Jick et al., 2000; Rajanikant et al., 2007). Several studies have suggested a positive role of statins on psychological well being, including a reduced risk for depression (Downs et., 1993; Freedman et al., 1995). It has been reported that simvastatin may show the acute antidepressant effects in forced swim test in rats (Kilic et al., 2012). Statins are the most widely used cholesterol-lowering agents, acting as inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A reductase, which catalyzes the rate limiting step in cholesterol biosynthesis (Armitage, 2007). In addition to their effects on serum cholesterol levels, statins also appear to affect brain cellular mechanisms of lipid and non-lipid systems in a variety of ways (Cucchiara and Kasner, 2001). A cholesterol-lowering drug such as simvastatin is lipophilic in nature which efficiently facilitates its penetration through blood brain barrier and influences the brain levels of cholesterol (Tsuji et al., 1993).

Several clinical, pharmacological, genetic and molecular evidences demonstrated that G-protein coupled receptors (GPCRs) play a critical role in depression and its treatments (Catapano and Manji, 2007; González-Maeso and Meana, 2006), raising the possibility that GPCRs could become a potential target for the treatment of mood disorders. Likewise, as mentioned above the sensitization of D2-like dopamine receptors, members of GPCRs family, in the mesolimbic dopamine system may represent a ‘final common pathway’ in antidepressant action. Several studies also
confirm that function of dopamine transporter (DAT) can be affected by manipulating the membrane cholesterol (Jones et al., 2012).

It has been proposed that plasticity of neuronal pathways may represent as rate limiting process in the pathogenesis and treatment of depression (Duman et al., 1997; Duman et al., 1999) and such plasticity of neuronal pathways is altered in depression as a dysfunction in molecular adaptive pathways of intracellular cascades (Quiroz and Manji, 2002). These adaptive pathways are regulated by cytokines and growth factors including the neurotrophin family (NGF). Brain derived neurotrophic factor (BDNF), is one of the growth factor of neurotrophin family, known to play significant role in the action of antidepressant treatments. (D’Sa and Duman, 2002; Manji and Duman, 2001; Reid and Stewart, 2001). It has been reported that BDNF expression level was decreased in regions of the hippocampus in post-mortem tissue taken from suicide victims or patients with depression (Castrén and Rantamäki, 2010). Several studies in rodents have also reported that the down-regulation of the BDNF expression may be induced by chronic mild stress (Vaidya and Duman, 2001). Moreover, direct infusion of BDNF protein into the midbrain exerts antidepressant effects in two models of depression, i.e. the forced swim and learned helplessness models (Siuciak et al., 1996).

It has been reported that above mentioned molecular adaptive pathways of intracellular cascades in depression was also reported to be regulated by G-protein receptor coupled (GPCRs) second messengers (e.g. cAMP, Ca$^{2+}$, etc) (Quiroz and Manji, 2002) apart from NGF family. Hypercholesterolemia has been reported to be associated with such changes in neurotransmission and second messenger system (Ohvo-Rekilä et al., 2002). Further, several lipid rafts, a specialized membrane micro domains enriched in cholesterol, has been reported to have important role in the GPCRs signal transduction (Hazelwood et al., 2010). Hence, it has been proposed that hypercholesterolemia may produce alteration in the neurobiology of depression.
Several studies have suggested the direct involvement of dopamine in the transcriptional regulation of the BDNF gene (Ohta et al., 2003; Park et al., 2009). There are independent reports suggesting a possible involvement of exon II transcripts of BDNF in the actions of antidepressants (Dias et al., 2003).

Dopamine can exert its effects through G-protein coupled receptors of which dopamine D$_2$ like receptors activated the protein kinase C and Ca$^{2+}$/Calmodulin-dependent protein kinase which results into the activation of MEK/MAPK cascade. It has been also reported that such activation of Ca$^{2+}$/Calmodulin-dependent protein kinase by dopamine D$_2$ like receptors also stimulated the phosphorylation of transcription factor cAMP response element binding protein (p-CREB), a common target for antidepressant drugs (Yan et al., 1999).

It has been reported that regulation of HMG CoA reductase (HMGR) has been mediated through the process of phosphorylation and dephosphorylation. HMGR is most active in the dephosphorylated state and inactive in its phosphorylated state. HMGR is phosphorylated by AMP-activated protein kinase (AMPK). AMPK itself is activated via phosphorylation which is catalyzed by calmodulin-dependent protein kinase kinase-beta (CaMKKβ) (Thomas et al., 2012). In the context of pathway of cholesterol biosynthesis, as a feedback mechanism, there is a increasing the activity of the inhibitor of phosphoprotein phosphatase inhibitor-1 (PPI-1). PPI-1 can inhibit the activity of protein phosphatase 2C (PP2C) which remove phosphates from AMPK. This maintains AMPK in the phosphorylated and active state. Likewise, PPI-1 can inhibit the activity of protein phosphatase (PP2A) which removes phosphates from HMGR, respectively. This maintains HMGR in the phosphorylated and inactive state (Thomas et al., 2012). In similar manner, statins has also been reported to inhibit or inactivate the function of HMGR.
Based on such events, it has been hypothesized that the administration of various dopaminergic agents might activate CaMKKβ which has been involved in the pathway of cholesterol biosynthesis. The activation of CaMKKβ may undergo two postulated actions. First, CaMKKβ may further activate the AMPK in the same way as mentioned above so that, there may be a certain possibility that it may result into the phosphorylation of HMGR (inactive state or statin like effect) in similar manner as mentioned above. Second, CaMKKβ may induce the phosphorylation of transcription factor CREB (p-CREB) in similar manner as mentioned above. Studies indicate that p-CREB binds to the CRE-like element within the promoter region of BDNF and thereby inducing BDNF gene expression (Tao et al., 1998). In fact, it can be considered as the hypothesis which may indicate the possible involvement of dopamine or dopamine D2 like receptor in statin induced beneficial effect in depression or may indicate the possible interaction between dopaminergic pathway and mevalonate pathway, having its implication in the reatment of depression.

In the light of above, the objective of the work was to evaluate the role of dopamine in various animal models of depression. Further, we have investigated the correlation of lipids with depression by investigating the interaction of dopaminergic agents with lipid lowering drugs. Finally, in an attempt to elucidate the possible link and the mechanism of depression and lipid levels we investigated the status of BDNF genes in mice brain using RT-PCR.