INTRODUCTION

The term “stress” can be used in two ways: either to identify events or circumstances that are perceived adversely (stressors) or to describe the state induced by such events or circumstances (the stress reaction) (Selye, 1936). Stress is a response of organism’s reaction to restore the body’s normal behavior (McEwen, 2007). The purpose of the stress response is to maintain homeostasis (McEwen, 2000), which includes a series of physiological reactions such as endocrine activation (especially of the hypothalamo–pituitary–adrenal, HPA axis) and cardiovascular changes. Stress can have psychopathological sequelae on a prolonged and sustained stimulation.

The prolonged exposure of stress causes detrimental health effects such as neurodegenerative diseases (Alzheimer’s disease and depression) (Munhoz et al., 2008); skin problems (psoriasis) (Zhang et al., 2009); autoimmune disorders (rheumatoid arthritis) (Steptoe et al., 2007); gastrointestinal diseases (Caso et al., 2008) and cardiovascular diseases (cardiomyopathy and coronary artery diseases) (Geppert et al., 2010) etc. The World Health Organization (WHO) survey estimates that 3.96% population would be effected from chronic stress related disorders by the year 2020. The WHO study on psychiatric problems employed and diagnosed 26,000 human volunteers from different primary care units in 14 countries and reported that 10.4% patients suffered from stress and its related diseases (North and Pfefferbaum, 2013). Also, National Co-morbidity Survey (NCS) studied that 17.3% of the total normal human population suffered from major depression and 24.5% experienced stress associated diseases during sometimes in their lives (Wakefield and Schmitz, 2013).

Chronic stress induces activation of adrenal glucocorticoid and catecholamine release, and later hypothalamic-pituitary adrenal (HPA) axis that plays a crucial role in maintaining basal and stress related homeostasis (Landfield et al., 2007). HPA axis regulation occurs at the level of parvicellular
Introduction

subdivision of the hypothalamic paraventricular nuclei (PVN) (Chrousos and Gold, 1992). In response to chronic stress, hypothalamic neurons releases corticotrophin-releasing factors (CRF) and triggers subsequent secretion and release of adrenocorticotropin (ACTH) from pituitary gland. ACTH stimulation leads to secretion and release of corticosteroids from the adrenal glands. Circulating corticosteroids inhibit secretion of CRF and ACTH by negative feedback mechanism (McEwen et al., 1986). Relationship between corticosteroids and stress is now well known. Studies are carried out to measure stress induced corticosteroids secretion (cortisol in humans, and corticosterone in animals) and ACTH levels (Shansky and Lipps, 2013). There is now considerable evidence suggesting an importance of the limbic system, particularly hippocampus, as well as cortical areas, such as prefrontal cortex, in the regulation of HPA activity. This regulation is possible through an inhibitory role of these regions on HPA-axis (Pepin et al., 1989).

Oxidative stress has a crucial role in the neuronal degeneration of central nervous system and pathology of several neurodegenerative diseases (Hovattaa et al., 2010). The release of reactive oxygen species (ROS) is significantly increased under several stressful conditions (Liu and Schubert, 2009). The possible reason of stress-induced free radical augmentation is the increase in nitric oxide synthesis (Matsumoto et al., 1999). Stress is known to cause reduction of oxidative defense enzymes such as glutathione peroxidase, catalase and superoxide dismutase (Zaidi and Banu, 2004). This results into increased oxidative load which is critically involved in several stress related pathology of diseased state. Thus, this reaction causes a significant damage to brain structural areas (Jain et al., 1991). Oxidative stress also causes damage to different cells and tissues through cellular cascades like apoptosis (programmed cell death) and neuroinflammation (Greenlund et al., 1995). In human subjects, chronic stress induces a robust increase in neuro-inflammatory cytokines (IL-6 and IL-1) in the blood circulation (Steptoe et al., 2007). It has been reported that pro-inflammatory cytokines such as tumor necrosis factor (TNF-α) released after stress stimulus can initiate an inflammatory response (Bierhaus et al., 2003). Inflammatory cytokines are known to alter metabolic processes, neurotrophic factors,
Introduction

Glutamatergic excitotoxicity and apoptosis (Maes, 2008). Oxidative stress and neuroinflammation are known key mediators during stress and related problems. However, their exact cellular and molecular interactions during stress and other related problems such as depression and cognitive dysfunction are not clear yet.

Depression is one of the common psychiatric problems and has been estimated to be the second biggest contributor of the global load of neurological diseases and disability by the year 2020 (Pichot et al., 2010). Epidemiological evidence also shows that life event stressors are major liability factors for the cause of depression (Paykel, 2003). Exposure of rodents to chronic stress induces behavioral changes in animals that mimic human depressive symptoms that help to understand antidepressant drug action (Willner, 2007). It has been suggested that stress and altered monoamine, hypothalamic-pituitary adrenal (HPA) axis, brain-derived neurotrophic factor (BDNF), and neuroinflammation might be implicated in the pathogenesis of major depression (Aggarwal et al., 2010). Exposure to chronic stress could lead to reduction of hippocampal volume and vulnerability to subsequent episodes of depression as a result of decreased neurogenesis, increased remodeling of dendrites, and loss of glial cells (Coyle and Duman, 2003). It has been demonstrated that behavioral deficits and abnormalities in the neuroendocrine system during chronic stress, such as hyperactivity can be reversed by antidepressant treatment (Mizoguchi et al., 2002).

Poor cognitive performance is also a frequent risk factor associated with exposure to prolonged stress (Radley et al., 2004). There exist a multifaceted association between stressful situation, mind and body's reaction to stress, and onset of cognitive disturbances (Bhutani et al., 2009). Chronic stress is known to influence cognitive tasks in various psychiatric patients (Vanitallie, 2002). Chronic stress increases corticosterone secretion, which results in HPA axis dysregulation and impairment of hippocampus-dependent learning and memory process (Kurukulasuriya et al., 2004). Since hippocampus plays a vital role in controlling learning and memory functions, their selective vulnerability may cause a risk of memory dysfunction (Ozdemir
et al., 2005). Oxidative stress mechanism has been implicated in the pathogenesis of several neurodegenerative and neurological disorders. Damage caused by oxidative cellular injury and activated inflammatory response has been well reported (Halliwell, 2006). Secretion of corticosterone also triggers oxidative stress and ultimately leads to memory dysfunction (Sato et al., 2010). However, the exact relationship of chronic stress and its related neurological problems such as depression and cognitive dysfunction are not clearly understood. Besides, detailed research investigation in the view of molecular and cellular cascades targeting new pathways for the management of chronic stress and related problems are very much needed.

Animal models are the basic tools to understand the pathophysiology of any neurological disorders and for the exploration of newer therapeutics. The stress can be classified as acute or chronic depending on the duration of exposure to the stressors. In an attempt to replicate human stress, various animal models of chronic stress have been proposed, these models include; chronic unpredictable stress (CUS), olfactory bulbectomy (OBX) and mild traumatic brain injury (mTBI) model. Chronic stress is called as unpredictable when the subject is unaware of the type and time of the stress. Chronic administration of variable stresses, a procedure known as “chronic unpredictable stress”, is thought to be a useful experimental model to study stress related pathology (Willner et al., 1992). CUS is known to effect different regions of the brain which plays a critical role in spatial navigation and memory process (Churchwell et al., 2010). Chronic variable stress is also known to cause microglial activation, resulting into neuroinflammation. Neuroinflammation hypothesis has also been well reported in memory dysfunction (Farooq et al., 2012).

Olfactory bulbectomy (OBX) has been widely used as an experimental model of depression (Song and Leonard, 2005). Bilateral destruction of olfactory bulbs induces behavioral alterations which are not only limited to the sensory deficit but also includes hyperactivity, alterations in exploration and social behavior (Mucignat-Caretta et al., 2004). Different studies on bulbectomized experimental model suggest that there is good face validity
with human depressive disorder, especially with agitated depression (Kelly et al., 1997; Song and Leonard, 2005). The olfactory bulb extends to different brain regions such as cortex, amygdala and hippocampus; consequently removal of them causes neurological deficits in these projections and perhaps results into numerous neurobiological, biochemical and behavioral alterations (Song and Leonard, 2005). Moreover, OBX has also been suggested to increase pro-inflammatory cytokines particularly tumor necrosis factor (TNF-α) in different brain regions (Myint et al., 2007) and promotes pathological damage by accompanying inflammatory reactions (Song et al., 2009). Further, OBX alters hippocampal neurogenesis, an important pathogenic mechanisms involved in the pathogenesis of depression (Jaako-Movits et al., 2006). Since OBX-induced depression-like behaviour responds to chronic and not acute antidepressant treatment, thus OBX can be considered as one of most reliable experimental models to evaluate antidepressant drugs (Song and Leonard, 2005).

Mild traumatic brain injury (mTBI) is the leading cause of mortality and severe disability in young adults, predominantly caused by motor vehicle accidents (Prins and Hovda, 2003). Animal models of mTBI help significantly to understand the process of evaluating and understanding the complex physiologic, behavioral, and histopathological changes. Clinical research and animal studies from past several years have now established the principal mechanism of brain damage after head injury; whether it is direct impact or acceleration/deceleration types of injury. Direct impact results from striking the head with an object. In opposite to it, acceleration/deceleration brain injury results from unrestricted head movement after injury. Traumatic brain injury can be classified as primary (which occurs instantaneously after injury) and secondary, which follows a cascade of injuries and may emerge in hours to days after the initial traumatic impact. The secondary damage after head trauma plays a crucial role in regulating inflammatory responses leading to severe neurodegeneration (Cederberg and Siesjo, 2010). Cortex and hippocampus are the two brain structures prominently affected during head trauma injury (Tong et al., 2002). Since hippocampal neurons play an important role in the learning and memory functions, thus their selective
vulnerability may cause a risk of memory dysfunction (Ozdemir et al., 2005). Oxidative stress has been initially implicated in the pathogenesis of several neurological disorders. Damage caused by oxidative cellular injury and activated inflammatory response has been well reported (Halliwell, 2006). The existence of a vicious cycle involving free radicals and inflammatory cytokines in post-traumatic stress disorder has also been well demonstrated (Pall and Satterlee, 2001).

Chronic stress can be managed by both non-pharmacological as well as pharmacological approaches. Most of the time, patients initially start with non-pharmacological treatment such as meditation therapy, exercise, health diet, adequate sleep, avoiding alcohol, smoking etc. But pharmacological treatment is equally important in conjunction with non-pharmacological options particularly when non-pharmacological approaches are inadequate. Patients are initially treated symptomatically with different GABAergic (hypnotic and sedatives), antidepressants, antioxidants; plant based herbal drugs etc. However, all the pharmacological treatments have their own side effects and limitations. Therefore, it is very important to understand the stress pathology in the light of cellular and molecular cascades (oxidative stress, neuroinflammation, apoptosis etc) with the help of modern tool and techniques for the better management and treatment of chronic stress and related pathology such as cognitive deficits, depression etc.

Thus, the present research work is an attempt towards understanding and exploring various pathophysiological pathways/mechanisms involved in the neurobiology of chronic stress-induced neurological deficits (depression and cognitive loss) and to evaluate efficacy of various herbal drugs against these chronic stress related conditions.