**Mood depressive disorder (MDD)** is a biologically and genetically heterogeneous disorder influenced by environmental and psychological factors, and has significant burdens of disease from morbidity and mortality, and is among the leading causes of reduced quality of life throughout the world. The aim of this study is the literature review of possible biological causes and consequences of mental illness among the leading causes of reduced quality of life throughout the world.

**NATURAL BODY RESPONSES TO STRESS**

Stress is known to activate different neuronal circuits in the brain and induce multiple cellular changes. Researchers have tied inflammation as one of the body's natural response to stress.

The glucocorticoid receptor imbalance in Major Depressive Disorder (MDD) is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress.

**The physiological effects of environmental stress are adaptive and natural responses to situations perceived by the individual as a biological or physical danger, and have implications for mental and physical health. The result of these effects is adaptive behaviours such as “fight or flight”, activating the release of:**

- Glucocorticoids
- Epinephrine
- Norepinephrine
- Adrenaline

**The immune system** initiates a cascade of inflammatory processes to protect the body from injury or infection and promote healing.

- pro-inflammatory cytokines such as Interleukin (IL)-1, IL-2, IL-12, Interferon-gamma (IFNgamma) and Tumor Necrosis Factor alpha (TNFalpha)
- anti-inflammatory cytokines such as IL4 and IL10

**Inflammation** can be damaging to the organism when it is inappropriate or chronic, and it becomes uncontrolled that is what happens in depressive people. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress. For this reason, inflammation is regulated and controlled at several levels, mostly due to the physiological effects of environmental stress.

**The glucocorticoid receptor** is a nuclear receptor that binds to glucocorticoid in the cytoplasm to act as a transcription factor. GR is kept in inactive state, and once bind to glucocorticoid, induces a conformational change of the receptor that induces dimerization and it switch into active state. Then, translocation along with its ligand into the nucleus is produced and the DNA binding domain binds to glucocorticoid response elements (GREs) on the DNA to modulate specific gene transcription.

There are two isoforms of GR:

- GRalpha
- GRbeta

**Glucocorticoid receptor imbalance in MDD** has been found in many mental illnesses, especially in MDD.

**NEUROBIOLOGICAL BASIS OF MDD**

**Stress and depression**

The effect of chronic negative conditions seems to amplify the link between acute life events and depressive symptoms. Disturbances in the hypothalamic-pituitary-adrenal axis (HPA) is associated with depression neuropsychiatric abnormalities. SNS hyperactivity and increased levels of plasma catecholamines, primarily norepinephrine, are observed in mood patients with MDD. These elevated levels of Norepinephrine enhance the previous statements physiological effects of stress.

The hypothalamic-pituitary-adrenal axis (HPA) is a regulatory system, which integrates neural and endocrine functions. Under physiological and physiological stressors:

1. Amygdala is activated, neuronal projection to paraventricular nucleus (PVN)
2. PVN secret corticotropin releasing hormone (CRH)
3. CRH induces the release of adrenocorticotropic hormone (ACTH) from pituitary gland
4. ACTH stimulates glucocorticoid secretion from adrenal cortex
5. Glucocorticoid acts as a negative regulator of the HPA axis activity

**Increasing evidence show the association between elevated levels of inflammatory cytokines, GR impairment and MDD**

**Genetic variations** involved in the regulation of stress response, HPA axis activity, glucocorticoids negative feedback, and glucocorticoid levels have probably important influence on abnormal adaptation to stress and the risk of developing MDD. The heritability of major depression is likely to be in about 30%. Some single nucleotide polymorphisms may have effects on GR gene transcription and/or GR function.

- NR3C1: human gene coding for the GR
- FKBP5: genes for the FKBP5 binding protein, which regulates the GR sensitivity

**Authors have shown that antidepressants modulate GR function.** Funato, H. et al. found that the application of anti-inflammatory drugs along with an antidepressant, reduce transcription time of the GR alpha into the nucleus, where start its function. Moreover an increased in GR alpha mRNA by antidepressants has also been described in studies that have measured the effect of different classes of antidepressants treatments, such as Cholinesterase.

**References:**