Glucocorticoid receptor imbalance in Major Depressive Disorder

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Mood depressive disorder (MDD) is a biologically and genetically heterogeneous disorder influenced by environmental and psychological factors. Involves significant burden of disease from morbidity and mortality, and is among the leading causes of reduced quality of life throughout the world.

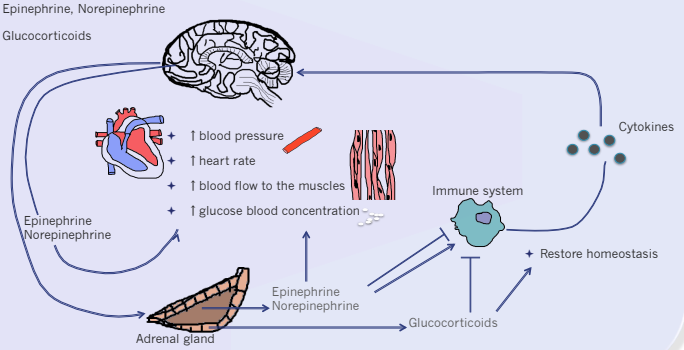
The aim of this study is the literature review of possible biological causes and consequences of mental illness depression, specifically the role of the GR mRNA expression.

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 **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:

- Epinephrine, Norepinephrine
- Glucocorticoids



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

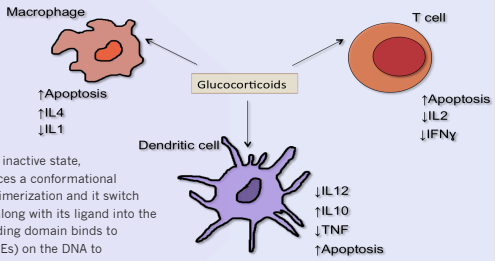
- pro-inflammatory cytokines such as Interleukin (IL1)-1, IL2, IL12, Interferon-gamma (IFNgamma) and Tumor Necrosis Factor-alpha (TNFalpha)
- anti-inflammatory cytokines such as IL4 and IL10

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 carried out by hormones called glucocorticoids that modulate immune responses through gene expression.

Once **Glucocorticoids** are released, its effect is finally determined by binding to central and peripheral Glucocorticoid receptor (GR). Glucocorticoids also bind to mineralocorticoid receptor (MR),

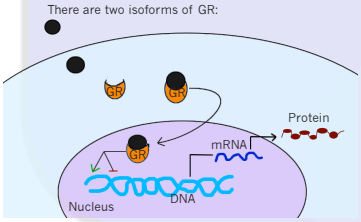
- MR has higher affinity and glucocorticoids can be easily attached in low concentrations to MR
- Glucocorticoids primarily bind to MR, and to GR when glucocorticoids levels increase, thereby MR is occupied during normal physiological conditions
- For this reason, GR is considered to be important in depression symptoms, in which glucocorticoids are present at extraordinarily high levels

→ Glucocorticoids are steroids that regulate inflammatory system



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:



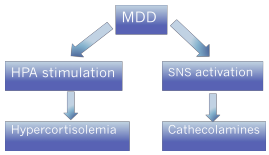
- Gralpha → acts as ligand activator of transcription factor
- Grbeta → acts as GRalpha Inhibitor

The **ratio imbalance GRalpha/GRbeta** has been found in many mental illnesses, especially in MDD.

NEUROBIOLOGICAL BASIS OF MDD

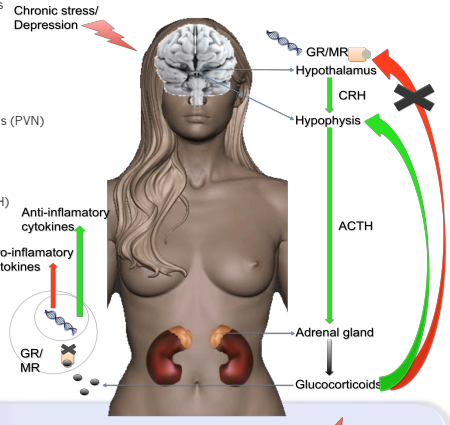
Stress and depression The effect of chronic negative conditions seems to amplify the link between acute life events and depressive symptoms.

Disturbances in the **sympathetic nervous system** (SNS) is associated with depression neuroendocrine abnormalities. SNS hyperactivity and increased levels of plasma cathecolamines, primarily norepinephrine, are observed in most patients with MDD. These elevated levels of Norepinephrine enhanced the previous statements physiological effects of stress.

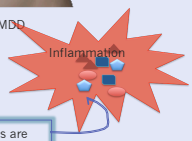


The **hypothalamic pituitary adrenal axis** (HPA) is a regulatory system, which integrates neural and endocrine functions. Under physical and physiological stressors:

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



- However, hyperactivity in HPA axis regulation has been associated with MDD
- Altered GR function and negative feedback regulation
- Increased glucocorticoid levels → Leading to partial glucocorticoid resistance
  - Effects of glucocorticoids on metabolic and immune functions are diminished



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

Tanapat P. study exposed pups rats to the odor of a known predator and examined plasma corticosterone (cortisol in humans) levels.

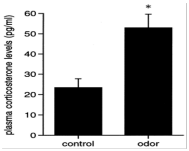


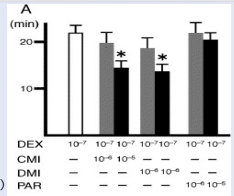
Figure1: The level of plasma corticosterone was elevated after odor exposure.
Ref: Tanapat P., et al. (1998)

Genetics 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.

- NR3C: human gene coding for the GR.
- FKBP5: gen codes 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 translocation time of the GRalpha into the nucleus, where start its function. Moreover, an increased in GRalpha mRNA by antidepressants has also been described in studies that have measured the effect of different classes of antidepressants treatments, such as Citalopram.

Ref: Funato, H. et al. (2006)



CONCLUDING COMMENTS

A large literature exists demonstrating that excess pro-inflammatory cytokines contribute to the depression symptoms by stimulating the HPA axis activity.

The results among several different scientific studies performed up to day about changes in the mRNA expression of the different isoforms of GR in patients with depression compared to control subjects show consensus on the decreases expression of GRalpha occurred in individuals suffering depression, and also on the GRtotal. However, there are highly variable levels of GRbeta mRNA expression between different articles in depressive patients. This shows the evident necessity of more scientific investigations on the role of GRbeta in HPA hyperactivity, inflammation and depressive symptoms.

All these findings generate an important key question: Is it GR impairment a consequence of depressive symptoms, or is it people who have GR malfunction more vulnerable to develop MDD?

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