Major depressive disorder: an integrative review of its neurobiology and therapeutic management

Rafael Moliner Herrero (rafael.moliner@e-campus.uab.cat)
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Introduction

The American Psychiatric Association (DSM-IV-TR) defines MDD as characterized by one or more depressive episodes with low depressive mood or lose of interest, anhedonia and a minimum of 4 depression symptoms persistent for at least 2 weeks.

MDD is one of the main causes of morbidity worldwide [1]:

- Prevalence tax is approximately 4% of the global population
- In most countries between 8-12% of the population will present at least one major depressive episode

My bachelor thesis aimed to:

1. Obtain an up-to-date neurobiological explanation for the onset, symptomatology and therapeutic management of the disorder that overcomes the limitations of the classical monoamine hypothesis
2. Integrate the knowledge about MDD to propose a coherent model for depression

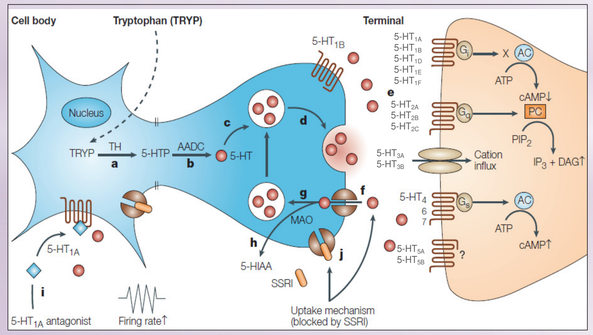

Figure 1. Schematic view of a serotonergic synapse. From: Wong et al., 2005

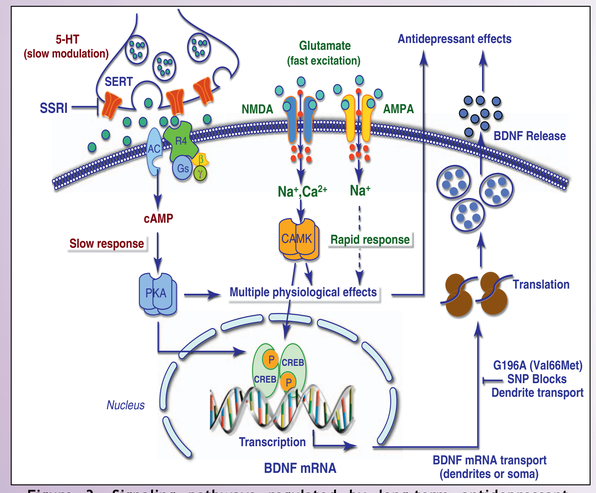

Figure 3. Signaling pathways regulated by long-term antidepressant treatment. From: Duman and Voleti, 2012.

Neurobiology of depression

Complex interaction of environmental and genetic factors is essential for the onset of MDD

Monoamine hypothesis

- Widely used to explain the neurobiology of MDD
- Main theoretical foundation for the use of conventional antidepressants

Postulates that depression is caused by decreased monoamine (5-HT, NE and DA) function in the brain as a result of their synaptic depletion (**Figure 1**).

Multiple limitations have been uncovered, motivating the research of complementary and alternative hypotheses [2].

The newest and most relevant hypotheses to explain the neurobiology of MDD are based on [2]:

- Abnormalities in anatomical and functional patterns of the depressed brain
- Role of neurogenesis and neuroplasticiy
- Disturbances of the endocrine system
- Neuroinflammation
- Climate conditions
- Glutamate hypothesis (?) Based on recent research

The monoamine hypothesis serves as a basis to explain many of the dysfunctionalities found in specific brain areas, and is intimately related to decrease in neurotropism (**Figure 2**) [3]. Nevertheless, neuroflamation and overactive HPA axis hypotheses are growing strong. And it is expected that a new one is formally put forward: the glutamate hypothesis [4]. All these pathologic mechanisms have localized effects on specific brain regions, globally resulting in abnormalities on large-scale brain networks that seem to be the reason for the behavioral changes in depression.

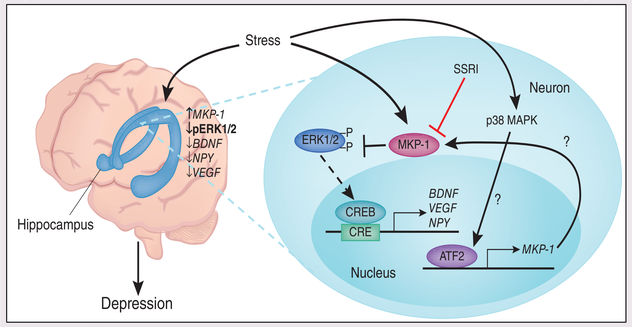

Figure 2. Effects of stress in the hippocampus. Increased MKP-1 hippocampal expression and activity under stress reduces CREB-dependent transcription of BDNF. BDNF signaling pathways lead to survival, growth and neuroplasticity. From: Schahram and Davis, 2010.

Therapeutic management

Pharmacotherapy is the most common treatment (**Figure 3**), usually in combination with psychotherapy. But antidepressant medication presents important limitations [5]:

- Most antidepressant drugs fail to show significant superiority to placebo, or represent just a small benefit
- Treatment-resistant depression is not rare

For these reasons, new therapies are being developed along with the neurobiological discoveries in depression, some of them with promising results [5]:

- ECT is often used in treatment-resistant cases
- DBS and rTMS are two experimental treatments that are showing promising results
- COX-2 inhibitors to treat neuroinflammation

There are many putative therapeutic targets that have yet to be explored, being remarkable the HPA axis and the hippocampus. In the later case, glutamate hypothesis and ketamine (a NMDA receptor antagonist) may be especially relevant due to the important role of this excitatory neurotransmitter in synaptic plasticity, and thus in learning and memory processes.

Proposed model for MDD

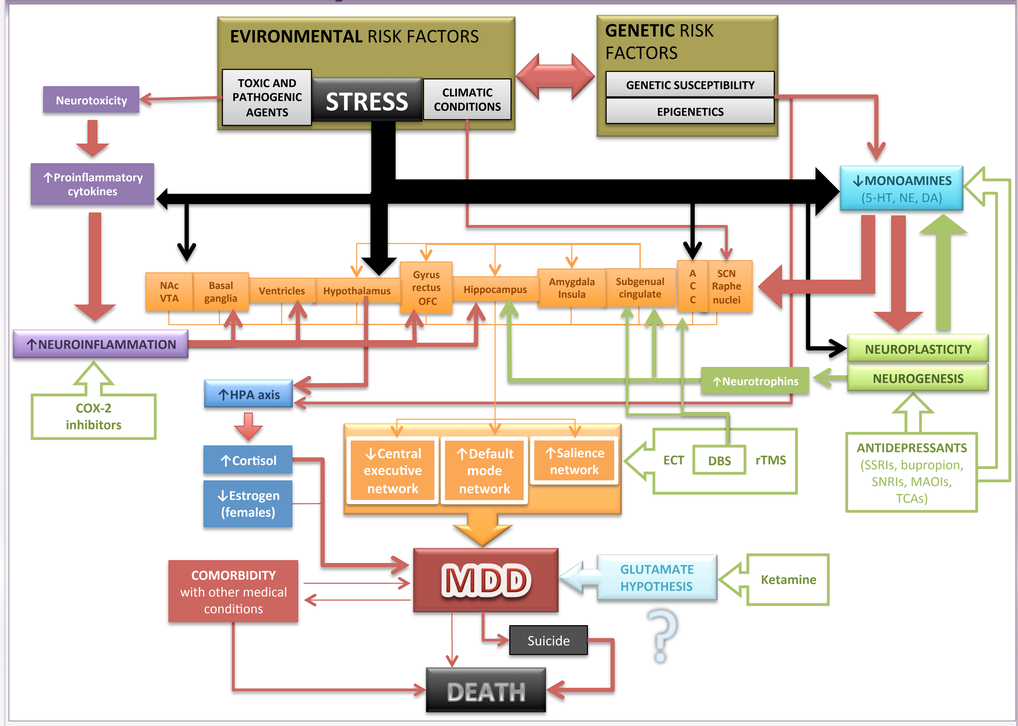

Figure 4. Interaction of different factors that lead to MDD and treatments for its management. Red arrow = pathologic connection; Green arrow = favorable/therapeutic connection. The thickness of the arrows indicates the relevance of the connections, being the thinnest the least relevant and the thickest the most relevant.

Conclusions

- MDD is far from being caused by a simple deficiency of central monoamines, a polysindromic nature of depression is deduced from the existence of multiple neurobiological hypotheses
- Publishing more realistic models of mental disorders serves as a starting point to develop new and more effective therapeutic strategies that explode the progress in neurobiological research
- Experimental treatments based in DBS, rTMS and ketamine are very promising; and if the research on the underlying genetics of psychiatric disorders continues to advance, it is not unlikely that we see gene therapy successfully implemented in psychiatry in the following decade

Abbreviations

5-HT: serotonin; BDNF: brain-derived neurotrophic factor; DA: dopamine; DBS: deep brain stimulation; ECT: electroconvulsive therapy; HPA axis: hypothalamus-pituitary-adrenal axis; MAOIs: monoamine oxidase inhibitors; MDD: major depressive disorder (also known as clinical or unipolar depression); NE: noradrenaline; rTMS: repetitive transcranial magnetic stimulation; SNRI: serotonin and noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

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